Validation of the iPad Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)

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1. Executive Summary

This executive summary provides an overview of this thesis which was submitted as part of the fulfilment for the Doctorate in Clinical Psychology. The subsections include the current executive summary, a systematic review, an empirical study and the integration, impact and dissemination summary section.

1.1. General background

The leading cause of neurodisability amongst young adults is Multiple Sclerosis (MS), which is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS) (Thompson, Baranzini, Geurts, Hemmer, & Ciccarelli, 2018). Cognitive impairment is amongst a constellation of symptoms in MS. Presentations vary and symptoms include fatigue, pain, vision problems, mobility difficulties, sexual problems, bladder and bowel difficulties and speech and swallowing difficulties.

Diagnosis is based on the most recent McDonald criteria, which has been recommended by the International Advisory Committee on Clinical Trials in Multiple Sclerosis (Thompson et al., 2017). Cognitive impairment remains absent from the diagnostic criteria for MS because of the difficulty of differential diagnosis with dementia. However cognitive impairment is experienced by half of individuals with

MS (Chiaravalloti & DeLuca, 2008) and it has major negative consequences for quality of life (Langdon, 2010). Therefore, cognitive assessment plays an important role in managing MS symptoms. Neuropsychological batteries are objective measures of cognition. Unlike patient self-report, neuropsychological batteries are not influenced by psychosocial factors like depression (Hanssen, Beiske, Landrø, & Hessen, 2014). They are more sensitive in detecting cognitive impairment in individuals with MS than clinical interviews (Romero, Shammi, & Feinstein, 2015) or Magnetic Resonance Imaging (MRI) (Rocca et al., 2015).

The most widely used neuropsychological battery was the Brief Repeatable Battery (BRB) (Rao & Group, 1990), followed by the more comprehensive Minimal Assessment of Cognitive Function in MS (MACFIMS) (Benedict et al., 2002). The batteries assessed a range of cognitive domains including Information Processing Speed (IPS), verbal and visual recall, attention, language and executive function through a variety of standardised tests. While these batteries offered several advantages to the validity of cognitive assessment over other techniques, issues emerged around the length of administration and the need for specialist training.

The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) (Langdon et al., 2012) was developed almost a decade ago to overcome these challenges, by maintaining sensitivity of assessment whilst reducing test duration and need for specialist training. In essence the BICAMS was designed to operate as a brief assessment of cognition for small centres without specialist expertise. The BICAMS assesses the three most common cognitive impairments in MS, which includes IPS, immediate verbal and visual recall. The BICAMS can be completed in

under 15 minutes and requires only papers, pencil and a stopwatch. Most healthcare professionals could administer the BICAMS.

1.2. Systematic Review

Shortly following the development of the BICAMS was the publication of the international validation protocol (Benedict et al., 2012). Several countries embarked on validating the BICAMS within their populations. The aim of the systematic review was to summarise the findings of the studies produced as part this international collaboration.

The keywords “multiple sclerosis” or “ms” were paired with “Brief International Cognitive Assessment for Multiple Sclerosis” or “BICAMS” in PubMed, PsycINFO, Medline and PsycArticles in January 2018. All titles and abstracts returned were examined against the following inclusion criteria: (a) peer-reviewed studies with no date restriction written in the English language; (b) samples including adults with any clinical subtype of MS (or subtype combination); and (c) studies which were undertaken as part of the international validation of the BICAMS protocol.

If the studies met the above criteria, then they were considered for the meta-analysis if they: (a) had a healthy control (HC) group; (b) reported standard quantitative information relevant to MS group and HC comparison group based on the subscales of the BICAMS: Symbol Digit Modalities Test (SDMT) for IPS (Smith, 1982); the California Verbal Learning Test II (CVLT-II) for immediate verbal recall (Delis, Kramer, Kaplan & Ober, 2000); and the Brief Visual Memory Test - Revised

(BVMT-R) for immediate visual memory (Benedict, 1997); and (c) that there were a minimum of four studies which met this criteria, as specified by Rosenthal (Rosenthal, 1991).

Sixteen studies met the criteria for the systematic review, of that total 14 were included in the meta-analysis. The authors extracted all of the relevant data. The quality of individual studies was rated by the authors (FC and DL) using the Effective Public Health Practice Project (EPHPP) (Thomas, Ciliska, Dobbins, & Micucci, 2004).

The findings showed that the BICAMS had been validated in 14 individual countries, including America, Argentina, Belgium, Brazil, Canada, Czechoslovakia, Greece, Hungary, Iran, Ireland, Italy, Japan, Lithuania and Turkey. As part of this process, the BICAMS was translated into 11 individual languages, including Czech, Dutch, Greek, Hungarian, Italian, Japanese, Lithuanian, Persian, Portuguese, Spanish and Turkish. The pooled sample size was 1,649 MS cases and 1,528 HCs. To provide an indication of representation, the sample size per study was compared to the total number of those with MS in each country using the Atlas of MS (Browne et al., 2014).

The contents of individual studies showed that gender ratio favoured females in every study but one. The gender ratio was only equal in two studies. The average age of participants was similar across studies. The mean age of people with MS was between 34 (sd= 10) to 45 years (sd= 9.93) and ranging between 34 (sd= 9.48) to 45 years (sd= 9.9) for HC. Diagnosis of MS was based on the best current standards (Polman et al., 2011). Similar inclusion and exclusion recruitment criteria were reported between validation studies, although there was minor evidence of

discrepancy. Relapsing Remitting MS (RRMS) was the most common disease course studied, compared to progressive forms of the condition. The illness duration ranged from 6 years (sd= 5.08) to 13 years (sd= 7.16). Overall the quality of studies were rated between 'Moderate' to 'Weak' based on the EPHPP template (Thomas et al., 2004).

In terms of the question about internal validity of the BICAMS across heterogeneous populations, cognitive ability was consistently shown to be reduced in people with MS compared to HC. This was demonstrated by the results of a random-effects meta-analysis. IPS was the largest cognitive deficit (g= 0.943, 95% CI= 0.839, 1.046, p < .001). In addition immediate recall was found to be impaired, but to a lesser extent. Immediate verbal recall, with a medium effect size (g= 0.671, 95% CI= 0.539, 0.804, p < .001) and recall of visual information with a medium effect size (g= 0.635, 95% CI= 0.534, 0.736, p < .001).

In conclusion, the review highlighted the extent to which the BICAMS had been validated internationally. Despite differences in study methodologies noted, the BICAMS was reliably shown to detect cognitive impairment in people with MS. This was most apparent in the domain of IPS. The BICAMS has been well evidenced as a standardised tool to assess the most common cognitive difficulties in MS.

1.3. Empirical Chapter

The iPad BICAMS was developed in 2018 to further improve cognitive assessment validity. The primary aim of this study was to establish the level of agreement

between the BICAMS iPad and the paper form. The level of agreement was expected to be high as all the physical parameters of the test were kept constant. Factors know to be associated with cognition in MS were expected to correlate with BICAMS scores. They included premorbid functioning, mood, fatigue, dexterity and visual functioning. The iPad BICAMS was thought to improve participant experience of cognitive assessments, thus it was hypothesised that participants would prefer iPad BICAMS.

Ethical approval was provided by the North East - Tyne & Wear South Research Ethics Committee (ref: 17/NE/0352) and certified by Royal Holloway Research Ethics Committee. The inclusion criteria were: (a) diagnosis of MS based on McDonald criteria or equivalent (Polman et al., 2011); (b) aged between 18 - 65 years; (c) be born and educated in England; and (d) able to give informed consent. The exclusion criteria were: (a) another primary neurological or psychiatric condition that might separately contribute to cognitive impairment; and (b) a sensorimotor impairment that would confound the testing performance.

The battery included nine elements. Premorbid functioning was assessed by the Test of Premorbid Functioning (TOPF) (Wechsler, 2011). Cognition was examined using two versions of the BICAMS (Langdon et al., 2012), the paper form and the newly developed iPad version. Self-reported depression and anxiety symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). Perceived fatigue was measured by the Fatigue Severity Scale (FSS) (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989). Dexterity was tested twice using the Nine-Hole Peg Test (9HPT) (Mathiowetz, Weber, Kashman, & Volland, 1985) and the

Grooved Pegboard Test (GPT) which has higher motor planning demands (Matthews & Klove, 1964). High Contrast Visual Acuity (HCVA), Low Contrast Visual Acuity (LCVA; at 2.5% and 1.25%) and Letter Contrast Sensitivity (LCS), were measured using the Multiple Sclerosis Vision Test Battery (MSVTS) (Bullimore, 2016). Participants completed a short survey to examine their experiences of undertaking BICAMS.

The study was a within-subjects cross-sectional counterbalanced randomised design. Using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) the specified sample size was 55 participants, holding an alpha at .05, with a power of .80. Data were investigated against the assumptions for parametric testing.

Forty individuals with MS completed the battery. The majority of the sample were female (n=27, 67%), in full-time employment (n=19, 48%) and had a diagnosis of RRMS (n=32, 80%). The average age was 45 (sd= 11.70). Duration of illness varied and the mean was 11 years (sd= 9.90). The average duration of education was 16 years (sd= 2.54). The sample had 'fair' mobility, according to the Hauser Ambulation Index ($\bar{x}$=2, sd=2.70).

The estimated level of premorbid functioning was in the 'average' range ($\bar{x}$= 110, sd= 12.25). Self-reported anxiety ($\bar{x}$=8, sd= 4.11) and depression ($\bar{x}$= 6, sd= 3.44) fell within the 'normal' to 'mild' range. Fatigue was above the threshold for suggested cut-off levels (m=42.75, sd=13.04). Dexterity was in the moderate range (9HPT, m=24 seconds, 7.3; GPT, m=111 seconds; sd=44). Visual functioning was better for HCVA (m=.10; sd=.17), which fell in the normal vision range, than it was for LCVA

(2.5%: m=.50, sd=.16; 1.25%: m=.73, sd=.10). LCS was below that signifying normal contrast sensitivity (m=1.89; sd=.21).

Three randomised intra-class correlations (ICC) confirmed the first hypothesis, they showed that the level of agreement was a satisfactory level between paper and iPad BICAMS. The ICC was greatest for the SDMT subscale (ICC = .85, 95% CI (0.74, 0.92), p < .001), followed by the BVMT-R (ICC = .67, 95% CI (0.45, 0.62), p < .001) and CVLT-II (ICC = .57, 95% CI (0.32, 0.75), p < .001). BICAMS iPad took 13 minutes (sd= 2.61) on average to complete. An order effect was observed in the CVLT-II. Participants performed more poorly if they received the paper version first (F (1, 39) 19.754, p < .001).

There was minimal support for the second hypothesis. Two significant correlations were found. The SDMT was significantly negatively associated with motor planning (r= -.469, p= .002). A linear regression revealed a significant relationship between SDMT and motor planning (p < .001). The R2 value was 0.22, thus 22% of the variation in SDMT could be explained by the model containing only motor planning. The BVMT-R was significantly negatively correlated with HCVA (r=-.459, p=.003). HCVA was within the normal range.

Support for the third hypothesis was mixed. The majority of participants (70%) reported that they would be 'moderately satisfied' to 'very satisfied' to be tested by BICAMS iPad on an annual basis. However they simultaneously expressed indifference between the types of BICAMS used. Therefore they were not unhappy with the iPad BICAMS and were as happy to complete it as the paper version.

In summary, the BICAMS iPad scores show at least a satisfactory level of agreement with the paper version. Limited power may explain the lack of correlations found between associated factors. Most participants would be 'moderately satisfied' to 'very satisfied' to be tested by BICAMS iPad annually. Therefore, with psychometric validation and participant endorsement, the BICAMS iPad could be used in routine clinical appointments in the future to monitor cognitive ability in MS.

1.4. Integration, Impact and Dissemination Summary

The subcomponents of the thesis will be disseminated in multiple formats to several audiences, including through scientific articles, conference posters and presentations and will be summarised by service-users on relevant MS specific websites. The chapters contained in this thesis are integrated well within the field of cognitive assessment in MS. Through international collaboration, the results of the systematic review show that the BICAMS has been standardised across heterogeneous samples and is a valid tool for assessing the most common types of cognitive impairment. The findings in the empirical study demonstrate the validity of the BICAMS iPad, which is arguably the next step in cognitive testing in MS. Overall these aspects highlight the feasibility, accessibility and effectiveness of brief cognitive assessment in MS, which have, up until now, been issues to address in the field.

2. Systematic Review

A systematic review and meta-analysis of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)

2.1. Abstract

Multiple Sclerosis (MS) is a neurological disease of the central nervous system (CNS). A large proportion of those affected will experience cognitive impairment, which is linked with a worse prognosis. Therefore cognitive assessment is vital. Neuropsychological batteries for MS were available to measure cognitive impairment. Yet, there were issues related to need for specialist equipment and training and the length of batteries. The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) was developed in 2010 as part of an international endeavour to optimise cognitive assessment. Several validation studies have been conducted as part of this project. The aim of this systematic review and meta-analysis was to synthesise literature published as part of the international validation protocol. A literature search was performed in PubMed, PsychoInfo and Google Scholar in January 2018. Sixteen studies met the inclusion criteria. A pooled sample of 1,649 adults with MS and 1,528 healthy controls (HC) were included in the review. The BICAMS was found to be widely validated across 11 different languages and in 14 individual cultures and locations. A meta-analysis was performed on 14 studies. The results showed that, compared to HC, adults with MS had significantly poorer

cognitive performance in all domains assessed by BICAMS, particularly in information processing speed. The most heterogeneous domain was immediate verbal recall, although this may have been related to language translation of the California Verbal Learning Trails II (CVLT-II). In conclusion the BICAMS has been shown to be a valid and reliable tool for assessing cognition in MS across heterogeneous samples at an international standard. Further validation studies are underway to support the protocol.

2.2. Introduction

2.2.1. Multiple Sclerosis

Multiple Sclerosis (MS) is the leading cause of neurodisability among young adults. There are approximately 127,000 people in the United Kingdom with the condition (Mackenzie, Morant, Bloomfield, MacDonald, & O'Riordan, 2014). MS is a chronic autoimmune, inflammatory neurological disease of the central nervous system (CNS) (Lublin, 2005). Inflammatory demyelination and, to a varying degree, axonal damage, underlies the condition (Thompson et al., 2018). Demyelination may lead to a reduction of conduction or complete failure of transmission. Axonal damage disrupts conduction, which produces symptoms when the slowing becomes critical (Katz, Sand & Lublin, 2013).

2.2.2. Clinical Features of Multiple Sclerosis

Neuropathic changes which result in damage to the CNS lead to a wide range of symptoms (Thompson et al., 2018), which include cognitive, motor, sensory, visual, bowel and bladder dysfunctions (Lassmann, 2010). Currently diagnosis of MS is based on the most recent McDonald criteria. The 2017 revisions were outlined by the International Advisory Committee on Clinical Trials in Multiple Sclerosis (Thompson et al., 2017). The guidelines stated that criteria for diagnosis of MS would require demonstration of dissemination of lesions in space (DIS) and time (DIT) and

the exclusion of alternative diagnoses based on a combination of clinical, imaging and laboratory tests.

2.2.3. Multiple Sclerosis Subtypes

There are four distinct MS disease courses (Achiron, Feldman, Magalashvili, Dolev, & Gurevich, 2012; Katz, Sand & Lublin, 2013; Thompson et al., 2018):

(a) Relapsing Remitting MS (RRMS): This is the most common form of the condition. This course involves a discrete episode, which can include the optic nerve, brainstem or spinal cord, followed by remission;

(b) Secondary-Progressive MS (SPMS): This is a progressive form of the disease, which accumulates disability. Approximately a third of individuals with RRMS will develop SPMS (15-30%), with or without superimposed relapses;

(c) Primary Progressive MS (PPMS): This course is progressive form from the outset, 15% of individuals with MS have PPMS;

(d) Benign MS: This will occur in a minority of individuals with RRMS (15%), compared to the other phenotypes this disease course was not thought to develop significant neurological disability.

2.2.4. Cognition in Multiple Sclerosis

Cognitive impairment is highly prevalent in MS. Almost half of those with the condition will have a cognitive deficit (Chiaravalloti & DeLuca, 2008). Cognitive

impairment occurs across all phenotypes (Potagas et al., 2008), yet it is more common in progressive forms of the disease (Papathanasiou, Messinis, Georgiou, & Papathanasopoulos, 2014). A review showed that neuropsychological presentations among patients with MS are influenced by a wide range of factors, including genetics, sex, intelligence, disease course, comorbid neuropsychiatric illness and health behaviours (Benedict & Zivadinov, 2011). Cognition in MS impacts on employment, disease management, personality, and many aspects of psychosocial function (Bruce, Hancock, Arnett, & Lynch, 2010; Kavaliunas et al., 2017; Roy et al., 2018).

2.2.5. Information Processing Speed in Multiple Sclerosis

Information Processing Speed (IPS) is the most prevalent cognitive impairment in MS (20 – 50%) (Grzegorski & Losy, 2017). This ability relates to the speed of processing a set amount of information (Kalmar & Chiaravalloti, 2007). The heterogeneity of previous study designs and tools to assess IPS have limited the ability to draw conclusions related to the nature of IPS dysfunction (Costa, Genova, DeLuca, & Chiaravalloti, 2016). It remains to be seen whether IPS represents the core cognitive deficit in MS (Denney, Lynch, Parmenter, & Horne, 2004), since it occurs concurrently with dysfunctions in other cognitive domains (Chiaravalloti & DeLuca, 2008).

2.2.6. Immediate Verbal Recall in Multiple Sclerosis

The second most typical cognitive impairment after IPS is verbal recall (33 – 65% prevalence) (Grzegorski & Losy, 2017). Many individuals with MS report difficulties with memory (Bobholz & Rao, 2003). Historically memory impairment was assessed though list-learning tests (e.g. (Rao, Hammeke, McQuillen, Khatri & Lloyd, 1984). Several previous meta-analysis have been conducted on verbal recall deficits in MS, however they are unable to provide a consensus regarding whether impairment relates to an acquisition or retrieval deficit (Lafosse, Mitchell, Corboy, & Filley, 2013 Prakash, Snook, Lewis, Motl, & Kramer, 2008; Thornton & Raz, 1997; Wishart & Sharpe, 1997; Zakzanis, 2000).

2.2.7. Immediate Visual Recall in Multiple Sclerosis

People with MS experience difficulties with visual recall (20% to 26% prevalence) (Vleugels et al., 2000). This dysfunction refers to memory of visual information (Chiaravalloti & DeLuca, 2008). Relatively few studies have investigated visuospatial ability in individuals with MS, compared to other deficits such as in verbal recall (Grzegorski & Losy, 2017). Visuospatial difficulties are associated with reduced speed of processing (Costa et al., 2016). An impairment in visuospatial ability may have consequences for more higher-order functions (Bruce, Bruce, & Arnett, 2007).

2.2.8. Other cognitive impairments in Multiple Sclerosis

There are a wide range of other cognitive functions which are impaired by MS. People with MS have difficulties in attention (12 – 25% prevalence) and executive functions (17-19% prevalence) (Grzegorski & Losy, 2017). People with MS show attention impairments across a range of tasks (Adler & Lembach, 2015; Beatty, Paul, Blanco, Hames, & Wılbanks, 1995; McCarthy, Beaumont, Thompson, & Peacock, 2005). In addition they show difficulties in higher-order cognitive processes (Santiago, Guardia, Casado, Carmona, & Arbizu, 2007) and cognitive flexibility (Parmenter, Shucard, & Shucard, 2007).

2.2.9. The impact of Cognitive Impairment in Multiple Sclerosis

Cognitive impairment has a significant negative impact on quality of life, which is over and above physical impairments (Langdon, 2010). Cognitive impairment interferes with participatory activities including, employability (Morrow et al., 2010) and driving (Lincoln & Radford, 2008). Service-user safety can become compromised, as cognitive impairment increases risk for falls (Gunn, Newell, Haas, Marsden, & Freeman, 2013) and ability to adhere to drug treatment (Bruce et al., 2010).

2.2.10. Cognitive assessment in Multiple Sclerosis

Routine evaluation of cognition is useful to support early identification of cognitive impairment and plays a role in the management of disease progression (Benedict &

Zivadinov, 2011). Until recently cognitive assessments in MS were only performed in university hospitals or specialist MS centres. Importantly cognitive assessment can be challenging to achieve for a number of reasons. Service-users' own self-report of cognitive ability is impacted upon by psychosocial variables, including depression (Hanssen et al., 2014). Clinical interviews, standard neurological examinations (Romero, Shammi, & Feinstein, 2015) and Magnetic Resonance Imaging (MRI) (Rocca et al., 2015) are not sensitive enough to detect cognitive impairment.

2.2.11. Neuropsychological batteries in Multiple Sclerosis

Neuropsychological tests are sensitive to cognitive impairment in MS. A few neuropsychological batteries have been developed to test objectively cognition in MS. In addition to these there are some brief assessment tools, which have been proposed to screen for cognitive impairment (e.g. Freitas , Batista, Afonso, Simões, de Sousa, 2016; Hansen et al., 2015; Hansen et al., 2017), although they differ in their validity and specificity of measurement and clinical thresholds.

For the three decades, the most widely used neuropsychological battery was the Brief Repeatable Battery (BRB) (Rao & Group, 1990). This BRB includes the Selective Reminding Test (SRT) (Buschke & Fuld, 1974) (for verbal memory), the Symbol Digit Modality Task (SDMT) (Smith, 1982) (for information processing speed), the Paced Auditory Serial Addition Test (PASAT) (Gronwall, 1977) (for information processing speed), the 10/36 Spatial Memory Test (SPART 10/36) (Barbizet & Cany, 1968), and Word List Generation (WL) (for language skills) (Spreen & Benton, 1969). The

administration time for the BRB is 45 minutes. The BRB has been validated in several countries and has been frequently used in pharmacological trials.

The Minimal Assessment of Cognitive Function in MS (MACFIMS) (Benedict et al., 2002) was developed as a more comprehensive assessment of cognition in MS. In the MACFIMS, the 10/36 SPART (Barbizet & Cany, 1968) is replaced by the Brief Visuospatial Memory Test Revised (BVMT-R) (Benedict, 1997) for visual memory and the SRT (Buschke & Fuld) with the California Verbal Learning Test II (CVLT-II) (Delis, Kramer, Kaplan & Ober, 2000) for verbal memory. The tests which are added are the Judgement of Line Orientation (spatial skills) (Benton, Hamsher, Varney & Spreen, 1983), the Delis–Kaplan Executive Function System (D-KEFS) (Baron, 2004) Sorting Task (executive skills – flexibility) and Controlled Oral Word Association Test (COWA, language) (Benton, Hamsher & Sivan, 1994). The administration time for the MACFMS is 90 minutes. Like the BRB, the MACFIMS has been validated in some other countries and has been used in research studies.

While these batteries are precise enough to capture cognitive ability across a number of domains, they require a trained neuropsychologist for administration. This reduces their feasibility for widespread routine clinical assessment (e.g. Santos, Pinheiro & Barros, 2015). These batteries are limited for multinational trial use, as there are only a few countries with validations outside of the United States.

2.2.12. Brief International Cognitive Assessment for Multiple Sclerosis

An expert consensus committee of seven neurologists and five neuropsychologists convened in June 2010 to develop recommendations for a screening assessment. The committee agreed to develop a brief monitoring tool, rather than cognitive screen or full assessment. Access and utility of the tool were among the primary concerns of the committee. To their knowledge, previous tests to evaluate cognition had not been internationally validated or standardised. The expert committee designed the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) to optimise the assessment of cognition in MS across international centres where neuropsychologists are not available (Langdon et al., 2012). The BICAMS could be used by most healthcare professionals working with people with MS.

The committee recommended that the BICAMS could be used for baseline and regular follow-up assessments which could be incorporated into routine clinical practice. The BICAMS was developed to be completed in less than 15 minutes. It does not require any special equipment (beyond paper, pens and a stopwatch). The committee critically evaluated the available cognitive scales and their psychometric properties. They decided that the BICAMS should assess the three most prevalent domains of cognition:

2.2.13. Symbol Digit Modalities Test (SDMT)

The Symbol Digit Modalities Test (SDMT) was selected to evaluate Information Processing Speed (IPS) (Smith, 1982). In the SDMT the participant is presented with a

record sheet which displays a nine-item key of single digits paired with abstract symbols. The digits are omitted from the remainder of the boxes. The participant is instructed to use the key to vocalise the corresponding numbers that should go in the empty boxes to match up with the symbols as fast as they can within a 90-second limit. The total number of correct responses is calculated to generate an overall score (maximum score possible is 110). The SDMT can be completed within 5 minutes, including the delivery of instructions, time allocated for practice and testing.

The oral SDMT has good construct validity (Christodoulou et al., 2003), sensitivity (78-82%) and specificity (60-69%) to cognitive impairment in individuals with MS (Camp et al., 1999; Deloire et al., 2006; López-Góngora, Querol, & Escartín, 2015; Parmenter, Weinstock-Guttman, Garg, Munschauer, & Benedict, 2007; Strober et al., 2009). As a tool the SDMT is highly sensitive to detect cognitive change (Amato et al., 2010; Holmén et al., 2011; Morrow et al., 2010).

The SDMT has the ability to distinguish adults with MS from Healthy Controls (HC) (Hughes, Denney, & Lynch, 2011; Langdon et al., 2012; O'Connell, Langdon, Tubridy, Hutchinson & McGuigan, 2015; Weinstock-Guttman, Morrow, Hojnacki Munschauer & Benedict, 2010). The SDMT has been broadly applied and the tool has been validated in several countries (Camp et al., 1999; Deloire et al., 2006; Strober et al., 2009). The SDMT shows good external utility, since it correlates with current (Einarsson et al., 2006) and future employment status (Morrow et al., 2010).

2.2.14. California Verbal Learning Test-II (CVLT-II)

The California Verbal Learning Test II (CVLT-II), five learning trials (Delis, Kramer, Kaplan & Ober, 2000) evaluates immediate verbal recall. The CVLT-II consists of a 16-item pseudo-randomised list of English words approximating a shopping list. Participants are instructed to recall as many words as possible, in any order, across a series of five trials. In the task the examiner reads each word out loud at a rate of one word per second. Participants are asked to respond with as many words as they can recall in every trial, including the words that they have already reported in previous trials. The words contained in the task were selected for their frequency of use across multiple demographic variables. The words belong to four semantically categorised groups: animals, transport, vegetables and office furniture. A total score is generated from the sum of the correct number of words reported across the five trials (maximum score possible: 80). Total time to administer the CVLT-II trials 1-5 is 5-10 minutes including instructions, testing and responses.

The CVLT-II shows good sensitivity (61%) (Niccolai et al., 2015) and specificity to cognitive impairment in MS (Strober et al., 2009). The CVLT-II has high test-retest reliability (Delis, Kramer, Kaplan & Ober, 2000; Benedict, 2005). The full scale version of the CVLT-II has been shown to be able to differentiate employed MS patients from patients not employed due to MS (Stegen et al., 2010).

The first five recall trials of the CVLT-II show a high degree of interdependence compared to other sections (Fink et al., 2010; Stegen et al., 2010) and thus the committee decided that they had sufficient psychometric rigour to be particularly

sensitive to MS impairment (Fink et al., 2010; Stegen et al., 2010). The psychometric properties outlined above should be considered as inferential as they do not utilise the other trials (including delayed recall, recognition, and category cued trials) (Langdon et al., 2012).

2.2.15. Brief Visual Memory Test – Revised learning trials (BVMT-R)

The Brief Visual Memory Test Revised (BVMT-R) learning trials (Benedict, 1997) assesses immediate visual recall. The BVMT-R comprises of 2 x 3 black geometric figures on a white background. Participants are instructed to observe the figures for the full display time of 10 seconds. The examiner removes the stimulus display from view. The participant is instructed to draw these shapes from memory in the correct position they were located on the stimulus sheet. This is repeated for three trials. Scoring is based on the accuracy of shapes and their location. The maximum scores possible is 12 for each trial, with an overall total of 36 possible for the whole task. The BVMT-R takes under 5 minutes to complete, including the instructions, display of the geometric figures and drawing time.

The BVMT-R is highly sensitive to detect cognitive impairment in MS (60) (Benedict, Priore, Miller, Munschauer & Jacobs, 2001; Langdon et al., 2012; Niccolai et al., 2015). The BVMT-R has good concurrent validity, as it correlates strongly with measures of explicit memory (r= .65 to .80) (Benedict, Schretlen, Groninger, Dobraski & Shpritz, 1996). Of note is that the psychometric properties of the assessment

should be considered inferentially, as the full scale version was not administered (Langdon et al., 2012).

2.2.16. Aim

In summary, cognitive impairment in MS has a significant negative impact on quality of life. Thus cognitive assessment is vital. The BICAMS was developed as a brief monitoring tool to assess the three most prevalent forms of cognitive impairment in MS, which include IPS and immediate and verbal and visual memory. The BICAMS overcomes several caveats of alternative forms of cognitive assessment in MS, including difficulties with patient report, and lack of sensitivity with clinical interview and MRI metrics. Neuropsychological batteries were developed to assess cognition in MS, although there are issues around access, including requirements of specialist training, specialist equipment and the test battery is lengthy.

The BICAMS committee published an international validation protocol (Benedict et al., 2012) which outlines five criteria by which the BICAMS can be validated in other languages to facilitate comparison across settings. In the second conference the committee agreed that most normative data had been based on US samples, which increased interpretative error when referenced to raw scores derived from a different culture, language or country. Therefore the committee outlined validation criteria which was to (a) standardise test stimuli for the culture or language; (b) standardise and translate examiner instructions; (c) recruit a minimum sample of 65 healthy controls matched to patients demographic; (d) establish test-retest reliability

over 1-3 weeks; and (e) establish criterion validity by comparing patient with control scores. The aim of the current systematic review and meta-analysis was to be the first to synthesise the BICAMS validation literature to investigate its accessibility. The meta-analysis is necessary for two reasons. Firstly, to calculate the effect size in cognitive impairment between MS cases and controls. Secondly, to understand the consistency of these effect sizes across different populations.

Research questions

Systematic Review

How many countries have participated in the international validation of the BICAMS and what do their data show following translations of the BICAMS?

Meta-analysis

What are the effect sizes of the BICAMS subscales of cognitive impairment between MS cases and controls?

2.3. Method

A search in the Cochrane Database in January 2018 confirmed that no previous reviews had been published in the proposed area. Thus the current review is the first attempt to synthesise studies published as part of the international validation of the BICAMS. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses

(PRISMA) Statement (Moher et al., 2009) were followed for standardised undertaking and reporting of reviews.

2.3.1. Systematic Literature Search

The search terms “multiple sclerosis” or “ms” were paired with “Brief International Cognitive Assessment for Multiple Sclerosis” or “BICAMS” to identify studies which were conducted as part of the international validation protocol of the BICAMS. These keywords were searched for within the Title or Abstract of the databases PubMed, PsycINFO, Medline and PsycArticles in January 2018.

2.3.2. Eligibility Criteria

The following inclusion criteria for the current review were to be: (a) peer-reviewed studies with no date restriction written in the English language; (b) samples including adults with any clinical subtype of MS (or subtype combination); and (c) studies which were undertaken as part of the international validation of the BICAMS protocol. Studies which included the BICAMS, but were not part of the international validation of the BICAMS protocol, were excluded. This criterion was necessary to allow for investigation of a set of studies which were methodologically matched according to the guidelines set out in the international validation protocol (e.g. test order administration, instructions).

If studies met the above criteria for review, they were considered for meta-analysis inclusion if they included: (d) a healthy control (HC) comparison group; (e) reported standard quantitative information based on the subscales of SDMT, CVLT-II and BVMT-R (mean, standard deviation and sample size) of the MS cases and HC comparison group; and (f) that there were a minimum of four studies, as specified by Rosenthal (Rosenthal, 1991), which met the criteria to be included in a meta-analysis.

All titles and abstracts which were returned in the search were screened to examine the eligibility criteria. The full-texts of articles that met the eligibility criteria were accessed as part of the screening process (see Figure 1).

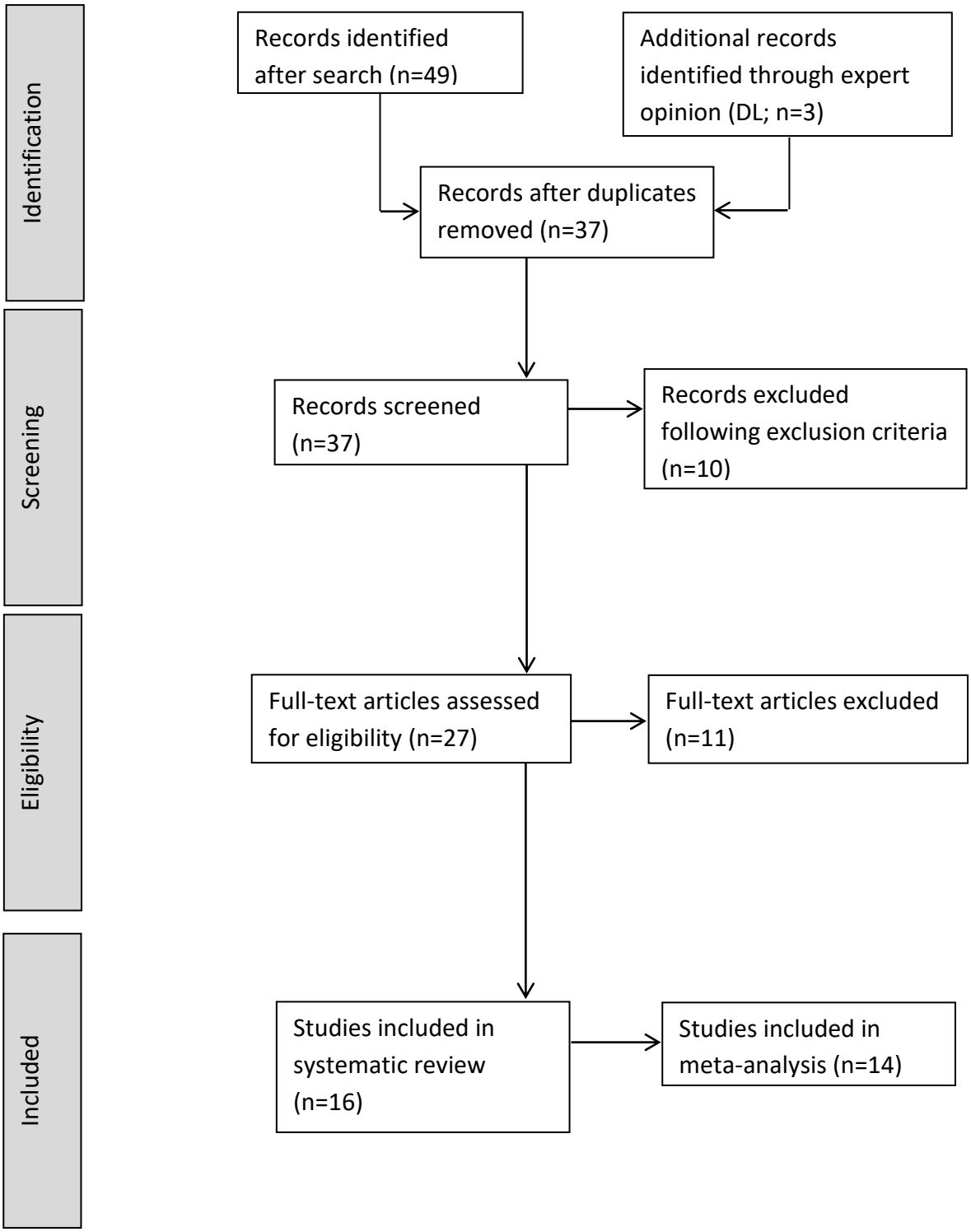


Figure 1. PRISMA flowchart for selection process of studies in systematic review and meta-analysis

2.3.3. Data extraction

A headed table was used to guide the extraction of relevant information from articles in a consistent manner to assess their eligibility for inclusion in the review. The studies were extracted and organised by the authors (FC and DL) according to whether they met criteria for the systematic review and/or the meta-analysis. Three studies were identified through expert opinion (DL), one study was in press at the time of search (Niino et al., 2018) and in the two remaining articles the BICAMS was completed as part of a comprehensive test battery (Eshaghi et al., 2012; Strober et al., 2009). A total of 21 studies were excluded from the final review following data extraction. Sixteen studies were shortlisted. Several socio-demographic and clinical characteristics were extracted from these studies. These comprised of recruitment selection, diagnostic criteria, participant age, MS phenotype, MS disease duration and time since diagnosis of MS, years of education, score on the Expanded Disability Status Scale (Kurtzke, 1983) and characteristics of the control group.

Of the above shortlisted studies, 14 studies included met the criteria for the meta-analyses. The standard quantitative information based on the subscales of SDMT, CVLT-II and BVMT-R (mean, standard deviation and sample size) of the MS cases and HC comparison group were extracted from these studies for the meta-analysis. All of the relevant data included in the current review and meta-analysis were obtained from information presented in text, tables and graphs.

2.3.4. Quality assessment

The Effective Public Health Practice Project (EPHPP) (Thomas et al., 2004) is an instrument which shows good test re-test reliability to examine the quality of studies in health care settings (Armijo-Olivo, Stiles, Hagen, Biondo, & Cummings, 2012). The EPHPP was used to rate the quality of studies included in the review. The EPHPP broadly examines quality of studies based on: selection bias, study design, confounders, blinding, data collection methods, and withdrawals or drop-outs. A total study quality score is based on the sum of the ratings for each of these dimensions. The two authors (FC and DL) independently rated studies according to the EPHPP and any disagreements were discussed and resolved.

2.3.5. Statistical analysis

The statistical software program Comprehensive Meta-Analysis version 3 (Borenstein, Hedges, Higgins & Rothstein, 2005) was used to perform three meta-analysis based on the averages of the subscales of SDMT, CVLT-II and BVMT-R. These subscales measure information processing speed, immediate verbal recall and visual recall respectively. Effect sizes were calculated as standardized mean differences with Hedges' g and were interpreted within the following parameters: 0.2 = small; 0.5 = medium; 0.8 = large. Hedges' g was selected for this analysis as it corrects for any potential biases that occur from small sample sizes and because it offers the same interpretation as Cohen d (While Cohen's d tends to overestimate the absolute

value of the standardized mean difference in small samples) (Hedges, Pustejoysky & Shadish, 2012).

The random-effects model was selected to examine how much the MS group differed from the HC based on their performance across the former BICAMS subscales. The random effects model was selected over the fixed effects model as it assumes the observed estimates of treatment effect vary across studies due to actual differences in the treatment effect in each study as well as sampling variability (Riley, Higgins & Deeks, 2011). In the present study there could be variation within MS samples as a result of heterogeneous presentations (Disanto et al., 2011).

The predicted direction was that adults with MS would have inferior cognitive performance across all subscales in contrast to HC. The random-effects model estimates a mean of a distribution of effects. Compared to the fixed-effect model, the random-effects model assumes that the allocation of study weights is based on the inverse of the total variance, which includes both within and between study variance. The fixed-effect model yields a wider confidence interval (CI) when there is significant heterogeneity among effect sizes.

Two statistics were performed to examine heterogeneity, Cochrane's Q was applied to examine for the presence of heterogeneity and the I^2 statistic to investigate for the magnitude of heterogeneity. A significant Cochrane's Q statistic indicates that variance occurring in the results may be due to dissimilar effect sizes across the studies included and sample or methodological differences. The proportion of the I^2 statistic can be interpreted as a small (25%), moderate (50%) or high (75%) level of

heterogeneity across studies and not due to random error (Higgins, Thompson, Deeks & Altman, 2003).

Forest plots were created to display the effect sizes for each study. In addition they were visually inspected for the presence of any outliers. Further sensitivity analyses were performed to assess for publication bias. Funnel plots of standardized mean differences against standard error were produced and tested against Egger's test of funnel plot asymmetry (Egger, Smith, Schneider & Minder, 1997) and Rosenthal's fail-safe N (Rosenthal, 1991). If publication bias was indicated by a significant Egger test (Egger regression test: $p < 0.1$), then the trim and fill method (Duval & Tweedie, 2000) for random-effects models was used to impute 'missing studies'. This method compensates for funnel plot asymmetry with the adjusted pooled effect sizes and 95% CIs reported after the addition of potential missing studies.

2.4. Results

2.4.1. Systematic review of BICAMS validation studies

Presented in Table 1 are the details of the sixteen studies which met the criteria to be included in the systematic review. The international validation protocol for BICAMS has been widely applied across 14 different countries, including America, Argentina, Belgium, Brazil, Canada, Czechoslovakia, Greece, Hungary, Iran, Ireland, Italy, Japan, and Lithuania and Turkey. The BICAMS was validated twice in both Italy and Argentina. Through the international validation process the BICAMS has been translated extensively from its original form in English into 11 individual languages:

Czech, Dutch, Greek, Hungarian, Italian, Japanese, Lithuanian, Persian, Portuguese, Spanish and Turkish. The systematic review is organised by providing an overview of the results of the systematic review and then a detailed summary of each study for reference.

Table 1. *Study design and participant demographics of international validation studies.*

Reference (first author, date)		N	Age m (sd)	Sex (% f)	Education m (sd)	Phenotype (% RRMS)	Duration m (sd)	EDDS m (sd)	SDMT m (sd)	CVLT-II m (sd)	BVMT-R m (sd)
Costers (2017)	MS	97	45 (10)	70	14 (2)	84	13 (7)	4 (3)	61 (10)	61 (60)	28 (5)
	HC	97	44 (13)	77	15 (2)	-	-	-	52 (13)	60 (13)	25 (29)
Dusankova (2012)	MS	369	34 (10)	68	14 (3)	68	8 (7)	3 (2)	50 (13)	60 (8)	23 (7)
	HC	134	34 (9)	71	14 (3)	-	-	-	65 (9)	52 (11)	29 (4)
Eshaghi (2012)	MS	156	34 (9)	71	14 (3)	80	6 (5)	3† (8)	44 (17)	49 (10)	21 (8)
	HC	90	34 (9)	63	14 (4)	-	-	-	56 (16)	55 (8)	25 (7)
Giedraitienė (2015)	MS	50	39 (10)	32	16 (3)	88	12 (10)	3 (1)	43 (14)	56 (10)	23 (7)
	HC	20	37 (16)	10	18 (4)	-	-	-	58 (12)	66 (6)	30 (4)
Goretti (2014)	MS	-	-	-	-	-	-	-	-	-	-
	HC	23 243	39 (13) 38 (13)	66 65	15 (3)	-	-	-	56 (11)	56 (9)	28 (6)

Table 1. *Continued.*

Reference (first author, date)		N	Age m (sd)	Sex (% f)	Education m (sd)	Phenotype (% RRMS)	Duration m (sd)	EDDS m (sd)	SDMT m (sd)	CVLT-II m (sd)	BVMT-R m (sd)
Niccolai (2015)	MS	192	41 (11)	74	12 (4)	100	13 (2)	3 (2)	46 (13)	50 (12)	24 (8)
	HC	200	-	-	-	-	-	-	56 (11)	56 (9)	28 (6)
Niino (2018)	MS	156	41 (10)	69	14 (2)	88		2 (2)	48 (14)	49 (13)	24 (8)
	HC	126	39 (12)	72	14 (2)	-	-	-	61 (10)	56 (11)	28 (5)
O'Connell (2015)	MS	67	44 (12)	73	14 (3)	70	10 (9)	2 (1)	46 (13)	45 (10)	18 (7)
	HC	66	43 (13)	68	14 (3)	-	-	-	56 (11)	54 (9)	21 (7)
Ozakbas (2017)	MS	173	38 (11)	71	14 (7)	87	9 (6)	2 (2)	43 (13)	46 (11)	17 (9)
	HC	153	37 (9)	71	15 (9)	-	-	-	54 (10)	54 (8)	23 (9)
Polychroniadou (2016)	MS	44	40 (10)	61	14 (5)	77	10 (4)	-	45 (17)	56 (12)	19 (8)
	HC	79	36 (11)	61	15 (6)	-	-	-	61 (13)	61 (11)	22 (7)
Sandi (2015)	MS	65	42 (9)	75	n=34 > 13 yrs	100	11 (8)	3 (2)	56 (16)	55 (11)	23 (9)
	HC	65	41 (12)	75	n=34 > 13 yrs	-	-	-	67 (12)	59 (8)	27 (6)

Table 1. *Continued.*

Reference (first author, date)		N	Age m (sd)	Sex (% f)	Education m (sd)	Phenotype (% RRMS)	Duration m (sd)	EDDS m (sd)	SDMT m (sd)	CVLT-II m (sd)	BVMT-R m (sd)
Spedo (2015)	MS	58	41 (12)	69	13 (6)	100	8 (7)	2 (2)	36 (16)	42 (12)	20 (9)
	HC	58	40 (12)	55	13 (4)	-	-	-	47 (13)	53 (11)	24 (8)
Strober (2009)	MS	65	45 (10)	80	14 (2)	72	10 (8)	3 (2)	48 (10)	48 (10)	26 (6)
	HC	46	45 (10)	85	15 (2)	-	-	-	62 (11)	57 (8)	21 (6)
Vanotti (2017)	MS	50	43 (10)	74	15 (3)	78	13 (9)	3 (3)	45 (16)	51 (12)	21 (8)
	HC	-	-	-	-	-	-	-	-	-	-
Vanotti (2016)	MS	50	43 (10)	74	15 (3)	78	13 (9)	3 (3)	45 (16)	51 (12)	21 (8)
	HC	100	42 (10)	75	15 (2)	-	-	-	57 (11)	61 (10)	23 (6)
Walker (2016)	MS	57	45 (10)	72	15 (3)	77	10 (8)	3 (2)	50 (11)	52 (10)	27 (7)
	HC	51	42 (11)	86	16 (2)	-	-	-	59 (8)	58 (8)	30 (4)

Note. Brief Visuospatial Memory Test Revised (BVMT-R); California Verbal Learning Trials II (CVLT-II); Expanded Disability Status Scale (EDSS); f (female); Healthy Control (HC); m (mean); Multiple Sclerosis (MS); RRMS (relapse remitting multiple sclerosis); sd (standard deviation); Symbol Digit Modalities Test (SDMT); yrs (years); †=median value.

2.4.2. Quality rating

According to the EPHPP template (Thomas et al., 2004) the overall quality rating of studies included in the review ranged from 'Moderate' to 'Weak'. Presented in Table 2 are the quality ratings for the studies included in the systematic review. The EPHPP examines ratings in quantitative studies according to: selection bias, study design, confounders, blinding, data collection methods, and withdrawals or drop-out. A total quality rating can be derived from the individual ratings of the measures, which is shown in the final column.

Table 2. Quality assessment of studies validating the BICAMS

Study (first author, year)	Selection bias	Study design	Confounders	Blinding	Data collection method	Withdrawals and drop out	Overall quality rating
Costers (2017)	Strong	Moderate	Strong	Weak	Strong	Strong	Moderate
Dusankova (2012)	Strong	Moderate	Strong	Weak	Weak	Strong	Weak
Eshaghi (2012)	Strong	Moderate	Strong	Weak	Weak	Strong	Weak
Giedraitienė (2015)	Strong	Moderate	Weak	Weak	Weak	Strong	Weak
Niccolai (2015)	Moderate	Moderate	Weak	Weak	Weak	Strong	Weak
Niino (2018)							
O'Connell (2015)	Strong	Moderate	Strong	Weak	Strong	Strong	Moderate
Ozakbas (2017)	Strong	Moderate	Strong	Weak	Strong	Strong	Moderate
Polychroniadou (2017)	Strong	Moderate	Weak	Weak	Weak	Strong	Weak
Sandi (2015)	Strong	Moderate	Weak	Weak	Weak	Strong	Weak
Spedo (2015)	Moderate	Moderate	Strong	Weak	Weak	Strong	Weak
Strober (2009)	Strong	Moderate	Strong	Weak	Strong	Strong	Moderate
Vanotti, (2017a)	Strong	Weak	Strong	Weak	Weak	Strong	Weak
Vanotti (2017b)	Strong	Moderate	Strong	Weak	Weak	Strong	Weak
Walker (2016)	Strong	Moderate	Strong	Weak	Strong	Strong	Moderate

Overall quality rating: Strong = no weak ratings; Moderate = one weak rating; Weak = two or more weak ratings.

2.4.3. Sample recruitment

MS participants were recruited to take part in the international validation protocol from a variety of sources, including university hospitals, MS centres, specialist clinics and tertiary referral centres, while HC were sampled from the community, were part of a normative sample or were known to the MS cases.

2.4.4. Sample size

The pooled sample size across the studies included was large. There were 1,649 adults with MS compared to 1,528 healthy controls. The Atlas of MS is the most extensive global study of the epidemiology of MS (Browne et al., 2014). Presented in Table 3 is the sample size per study which was compared to that of the number of individuals documented using the Atlas per country with MS. Almost all studies included a case and control comparison, thirteen studies included a group of adults with MS and HC, while two studies did not. The studies which deviated from this design included only a single group of MS cases or HC. The sample size varied between studies, this ranged from 369 MS cases to 44 and from 200 HC to 20. Only three studies contained equal sample sizes between cases and controls.

Table 3. *Comparison sample in BICAMS validation studies with actual number of individuals with Multiple Sclerosis (MS) in each country.*

Reference (first author, year)	Country	n per study	n per country	Percent represented
Costers (2017)	Belgium	97	12,000	0.81%
Dusankova (2012)	Czech Republic	369	16,000	2.31%
Eshaghi (2012)	Iran	156	50,000	0.31%
Giedraitienė (2015)	Lithuania	50	2,621	1.91%
Niccolai (2015)	Italy	192	68,000	0.03%
Niino (in press)	Japan	156	12,000	1.30%
O'Connell (2015)	Ireland	67	7,000	0.96%
Ozakbas (2017)	Turkey	173	40,000	0.43%
Polychroniadou (2016)	Greece	44	7,000	0.63%
Sandi (2015)	Hungary	65	20,000	0.33%
Spedo (2015)	Brazil	58	30,000	0.19%
Strober (2009)	United States	65	400,000	0.02%
Vanotti (2016; 2017)	Argentina	50	8,000	0.06%
Walker (2016)	Canada	57	97,366	0.06%

2.4.5. Gender

In the majority of studies the gender ratio was disproportionate, in the direction of females. MS is more common in females (e.g. Westerlind et al., 2014). In MS cases this ranged between 61% to 80% and 55% to 86% in the HC. A single study deviated from this representation, in this case there was a lower percentage of females in the sample than males (32% females with MS; 10% healthy females). The gender ratio was only equal in two studies (61% females and 75% HC).

2.4.6. Average participant age in years

The age of participants included in the review was relatively consistent with similar standard deviations. The mean ages of adults with MS reported across the studies ranged from 34 (sd= 10) to 45 (sd= 9.93) and for HC from 34 (sd= 9.48) to 45 (sd=9.9). The pooled age across studies was comparable, 39 years for adults with MS and 40 years for HC.

2.4.7. Diagnosis and selection criteria

The most common reported form of diagnosis of MS was through the revised McDonald criteria (Polman et al., 2011) or later versions. The studies reported consistent recruitment parameters based on similar inclusion and exclusion criteria. Most studies stated that they were able to match the MS cases with a HC comparison group.

2.4.8. Type of MS

RRMS was the most commonly represented MS phenotype across the studies included in the review. The other disease courses represented to a lesser extent were SPMS, RPMS, PPMS and CIS. Most studies included a mix of phenotypes in the MS sample, while three included only RRMS. In the studies that mixed subtypes, there were different numbers of representations for each phenotype.

2.4.9. Disease duration and time since diagnosis

The average disease duration varied between studies from 6.07 years (sd= 5.08) to 12.97 years (sd= 7.16).

2.4.10. BICAMS type and mode of delivery

The conventional paper version of the BICAMS was used in all studies. As detailed in the study summary descriptions below, the BICAMS demonstrates good reliability and ability to distinguish individuals with MS from HC controls, as estimates of cognitive impairment were detected in almost half of individuals with MS. Appropriate translations were made to the BICAMS and were validated as part of the international validation protocol. Three studies reported the profession of the BICAMS assessor, which included a neuropsychologist, an MS Nurse Specialist and a PhD Student. Most studies did not report who administered the BICAMS.

2.4.11. Individual study summaries

A short description of each study which was included in the systematic review is provided below, with the first author's name as reference to the paper.

Costers et al. (2017)

The aim of the study was to validate the BICAMS in a Belgian Dutch-speaking population and to investigate the validity of including extensive versions of two of the three BICAMS subtests. Ninety-seven MS patients were recruited from National MS Center Melsbroek and the Revalidation and MS Center Overpelt in Belgium. Exclusion criteria were a relapse in the last month before assessment, neurological screening in the last three months before the assessment, neurological disorders other than MS that influence cognitive functioning (e.g. dementia or brain injury), psychiatric disorders, that could influence cognitive performance or sensory or motor problems that could influence cognitive test performance. Ninety-seven healthy controls that were matched on age, education level and gender were recruited from friends or relatives of MS participants and from the personnel at the MS Center Melsbroek. Participants completed the SDMT and the full versions of the CVLT and BVMT-R, as well as the Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock & Erbaugh, 1961) and the Fatigue Scale for Motor and Cognitive Functions (FSMC) (Penner et al., 2009). A Dutch translation of the CVLT-II word list had been applied. Most of the sample had RRMS (84%). The results showed that only the SDMT and BVMT-R significantly distinguished individuals with MS from HC. MS performance on the CVLT-II indicated learning effects. They concluded that the extended versions of the CVLT-II and BVMT-R did not improve the psychometric properties of the BICAMS. Adults with MS were significantly more depressed than HC.

Dusankova, Kalincik, Havrdova & Benedict (2012)

The objectives defined in this study were to test validity of the Czech translations of the MACFIMS and the BICAMS and to compare outcomes of the BICAMS to the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) (Benedict et al., 2006) in a sample of Czech individuals with MS. A large sample of 367 patients were recruited from the MS Centre of the General University Hospital and the first Faculty of Medicine, Charles University in Prague and 134 healthy controls were also recruited. Exclusion criteria were defined as: current or previous neurological disorder other than MS, a, prior history of a psychotic disorder, a current psychiatric disorder, other than mood, personality, or behaviour changes following the onset of MS, a medical condition which influences cognition, a history of a developmental disorder, a history of or current substance or alcohol dependence, a motor or sensory defect that might interfere with cognitive test performance, or a relapse and/or corticosteroid pulse within 4 weeks of assessment. All participants completed the SDMT and the full versions of the CVLT and BVMT-R, as well as the MACFIMS, BDI and BAI (Beck et al., 1961). The BICAMS was sensitive to detect cognitive impairment in MS defined by the MACFIMS. Cognitive impairment was found to be associated with vocational status. Individuals with MS showed high levels of anxiety and depression compared to health controls.

Eshaghi et al. (2012)

The aim of this study was to validate Minimal Assessment of Cognitive Function in MS (MACFIMS) (Benedict et al., 2006) in Persian. There were 156 patients with MS who participated who had been receiving care in the MS Clinic at Sina Hospital in Tehran. Inclusion criteria for the study were for a diagnosis of MS by the revised McDonald criteria (Polman et al., 2005), the absence of neurologic/psychiatric diagnosis other than MS and MS-related behavioural changes, no IV corticosteroid use or MS relapse within six weeks of assessment, no history of a developmental disorder and no history of drug or alcohol substance abuse. The majority of the sample had RRMS (81%). Ninety matched for age, gender and education with healthy controls recruited from the community. All participants completed the SDMT and the full versions of the CVLT and BVMT-R as part of the complete MACFIMS. A subset of 41 patients completed the MACFIMS 10 days later for reliability analysis. The findings demonstrated that individuals with MS performed worse than HC on all aspects of the MACFIMS. The SDMT was identified as the most robust assessment. There were modest test re-test associations.

Giedraitienė & Kizlaitienė (2015)

The main objective of this study was to validate the Lithuanian translation of the BICAMS and to evaluate the test-retest reliability, and to estimate the impact of cognitive impairment on disability and duration of MS. Fifty patients with MS were recruited from Vilnius University Hospital Santariskiu Clinics. The inclusion criteria

specified that individuals with MS had a diagnosis based on the revised McDonald criteria (Polman et al., 2011) with no evidence of relapse for at least four weeks preceding participation in the study, no neurological or psychiatric disorder other than MS, no history of a developmental disorder, or visual or hearing problem which would confound performance on the battery, no cognition-enhancing medication (e.g., antidepressants, neuroleptics, and anticholinergic drugs) within the six months prior to taking part in the study and no current or past substance abuse. A total of twenty healthy control participants who were either the relatives of, and persons accompanying, the patients attending the Neurology Department were matched for age, gender and years of education. The majority of MS clinical cases had RRMS (88%). All participants completed the BICAMS Lithuanian translation. The results from the BICAMS show that individuals with MS scored significantly lower on all three subscales. The Lithuanian translation of the BICAMS had high test re-test reliability. Gender was not found to influence cognitive performance on the BICAMS. Years of education was found to significantly influence cognitive performance.

Goretti et al. (2014)

The objective of this study was to gather regression based normative data for the BICAMS battery in an Italian population. A large sample of 273 healthy controls was recruited from the community. The following exclusion criteria were applied: no history of a learning disability, or serious head trauma (causing coma and/or neuropsychological dysfunctions) and no history of alcohol or drug abuse as well as

major medical illness. The healthy sample completed the BICAMS Italian translation and at follow-up. A subset of 243 healthy controls participated in a follow-up assessment three weeks later. In the current study normative values with an Italian population were obtained.

Niccolai et al. (2015)

The main aim of this investigation was to compare the performance of BICAMS and Brief Repeatable Battery (BRB) (Rao & Cognitive Function Study Group & Society, 1990) in MS subjects. A large sample of 192 patients with RRMS subtype was recruited from 11 Italian centres. Exclusion criteria specific was current or past neurological disorder other than MS, major psychiatric illness, a history of a developmental disorder, a head trauma, a history of alcohol or substance abuse or a relapse and/or corticosteroid use in the previous 4 weeks. Participants completed both the BRB and the Italian translation of the BICAMS. Cognitive performance on the BICAMS and BRB was compared to that of normative health controls in Goretti's investigation (Goretti et al., 2014). Patients with RRMS had worse cognitive performance than the normative sample on both measures. There was a fair to moderate agreement between the BICAMS and the BRB on ability to distinguish HC from patients with MS, the SDMT was identified to be the strongest ability to indicate this difference.

Niino et al. (2018)

The aim of the study was to validate and assess the reliability of the BICAMS in the Japanese population. A sample of 156 patients with MS were recruited according to the revised McDonald criteria (Polman et al., 2011). One hundred and twenty six healthy controls were matched for age, gender and duration of education. Exclusion criteria were severe visual or motor disabilities, neuromyelitis optica spectrum disorders (NMOSD), significant relapses or the use of steroids within 1 month before the examination and no previous major psychiatric disorder or prescribed anti-psychotics. Most of the patients with MS had RRMS subtype (n=137). All participants completed the BICAMS Japanese translation. The findings showed that individuals with MS performed worse than healthy controls, particularly in the SDMT. Age at examination negatively correlated with cognitive performance on the BICAMS. Negative associations were recorded between educational level and the SDMT and CVLT-II subscales.

O'Connell et al. (2015)

The primary objective of this study was to validate the BICAMS in Irish patients with MS and healthy controls. Sixty-seven patients with MS according to the revised McDonald criteria (Polman et al., 2011) were recruited from a specialist clinic in a tertiary referral centre. Exclusion criteria were set as the following: a history of a neurological or psychiatric disorder, a concurrent medical condition that might influence cognition, a developmental disorder, a history of substance or alcohol

dependence, a visual, motor or sensory impairment that might interfere with cognitive test and a relapse or corticosteroid treatment within 4 weeks of taking part in the study. Sixty-six healthy control participants were recruited from unaffected relatives, spouses or carers and were matched by age, gender and years of education. Participants completed the BICAMS, Hospital Anxiety and Depression Score (HADS) (Zigmond & Snaith, 1983) and the Modified Fatigue Impact Scale (MFIS) (Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994). Patients with MS had higher rates of unemployment. The BICAMS was shown to discriminate patients with MS from HC in the current study.

Ozakbas et al. (2017)

The purpose of this study was to validate the BICAMS in a Turkish population. One hundred and seventy-three MS patients were recruited according to the 2010 revised McDonald criteria (Polman et al., 2011). The study applied the following exclusion criteria: no evidence of relapse, being steroid and/or plasmapheresis-free for at least 4 weeks, a history of a neurological disorder other than MS, a current psychiatric illness unrelated to that diagnosis, a coexistent medical condition, a history of developmental disorder, any vision or hearing problems and a history of alcohol or drug abuse. A total of one hundred and fifty three control participants, who were matched in terms of age, gender and years of education, were recruited from unaffected relatives or friends of MS patients or from other individuals attending the neurology outpatient clinic for other reasons. Participants completed

the BICAMS Turkish translation, the BDI (Beck et al., 1961), Modified Fatigue Impact Scale (MFIS) (Fisk et al., 1994) and the Multiple Sclerosis International Quality of Life (MUSIQoL) questionnaire (Simeoni et al., 2008). The BICAMS was repeated. Most the MS sample had RRMS (87%). The results from the BICAMS showed that MS patients performed significantly worse on all subsets compared to healthy controls. Cognitive impairment was demonstrated in 45% of patients. The BICAMS showed strong test re-test reliability. Disability and duration of disease was associated with severity of cognitive impairment.

Polychroniadou et al. (2016)

The objective of this study was to validate the BICAMS in a Greek population. Forty four patients with MS were recruited according to the revised MacDonald criteria (Polman et al., 2011), including those with Clinically Isolated Syndrome (CIS). Patients were included regardless of Disease Modifying Treatment (DMT) or a history of a major psychiatric illness. Seventy healthy controls were matched according to age, education, gender and premorbid cognitive reserve. All participants completed the Greek adaptation of the BICAMS and Cognitive Reserve Index questionnaire (CRIq) (Nucci, Mapelli, & Mondini, 2012) and again at follow-up. The findings showed that individuals with MS performed significantly worse than healthy controls. According to the BICAMS, 47% met the criteria for a cognitive impairment. Test re-test reliability was strong.

Sandi et al. (2015)

The aim of this study was to assess the validity of the BICAMS Hungarian translation and to evaluate this in relation to quality of life and its impact on cognitive status. Sixty-five patients with MS were recruited from the Department of Neurology of the University of Szeged. A comparison group of sixty-five HC were recruited and were matched for age, sex and years of education. All individuals with MS had RRMS subtype. Exclusion criteria were for acute relapse, alcohol abuse and a history of a psychiatric, mood or personality disorder. All participants completed the BICAMS Hungarian translation and at follow-up, the Fatigue Impact Scale(FIS)(Fisk et al., 1994) and the Multiple Sclerosis Quality of Life-54 (MSQoL54) (Fuvesi et al., 2008; Vickrey, Hays, Harooni, Myers, & Ellison, 1995). The results showed that individuals with MS performed significantly worse than healthy controls, apart from the CVLT-II immediate test. There was a modest test re-test correlation on BICAMS performance. 52% of individuals with MS were shown to have a cognitive impairment. Fatigue negatively correlated with cognitive performance. Cognitive impairment was adversely associated with several domains of quality of life, including physical functioning, social and cognitive functioning, general health scale, quality of life and sexual performance and satisfaction with sexual performance.

Spedo et al. (2015)

The primary objective of this investigation was to assess the validity of the BICAMS Brazilian-Portuguese translation. Fifty-eight MS patients were recruited from MS

Centres in Brazil and fifty-eight healthy controls were recruited from the community were matched on several demographic characteristics. All participants were free from a history of a neurological disease other than MS, had no prior psychiatric illness or depression emerging after the development of MS or history of substance or alcohol dependence. All MS patients had RRMS subtype and diagnosis of MS was based on the revised McDonald criteria (Polman et al., 2011). Individuals with MS had no acute relapse within the past 30 days. Participants completed the BICAMS Portuguese translation at two times, one at baseline and one at two weeks follow-up, as well as the Hospital Anxiety and Depression Scale (Herrmann, 1997). The findings showed that individuals with MS had significantly poorer cognitive performance on the BICAMS compared to healthy controls and this effect still stood even after the effects of depression, anxiety, education and age were removed. Test re-test associations ranged between good to excellent. Individuals with MS had higher rates of depression, but not anxiety, compared to healthy controls. Age negatively correlated with all BICAMS subscales whereas education was positively correlated with the performance on the instrument.

Strober et al. (2009)

The aim of this study was to examine the sensitivity of BRNB (Rao, 1991) and MACFIMS (Benedict et al., 2006) batteries in MS and to understand which measures best discriminate MS patients from healthy controls. This study was included in the review as it uses the BICAMS subscales. A total of sixty-five patients from the United

States were recruited to participate in the study. Forty-six health controls were matched for age and education. Exclusion criteria included a history of a neurological or psychiatric disorder other than MS, a current depressive episode, a history of a developmental disorder, a history of substance dependence, a motor or sensory defect that might substantially interfere with cognitive test performance or an acute relapse within 4 weeks of assessment. The majority of MS patients had RRMS (72%). Participants completed all aspects of the BRNB (Rao, 1991) and MACFIMS (Benedict et al., 2006) batteries, which included the SDMT, CVLT-II and BVMT-R. Participants with MS were shown to perform significantly worse on the SDMT and BVMT-R compared to healthy controls. Their complete performance on the CVLT-II did not discriminate them from healthy controls, patients with MS only performed significantly worse than healthy controls on the immediate delayed recall aspects of the test, but had similar performance on sematic and serial clustering. The MACFIMS was found to a have marginally better ability to discriminate individuals with MS from healthy controls (83%) compared to the BRNB (79%).

Vanotti et al. (2016)

The aim of this study was to validate the BICAMS in Argentina and to obtain normative data in Spanish for this population. Fifty participants with MS were recruited for the study. Diagnosis was made according to the revised McDonald criteria (Polman et al., 2011). The majority of the sample had RRMS subtype (78%). One-hundred healthy control participants were recruited from the community and

were matched in terms of age, years of schooling and gender. Elusion criteria included the following: current or previous neurological disorder other than MS, history of psychotic or psychiatric disorder, a medical condition that might affect cognition, a history of developmental disorder, a history of substance or alcohol abuse, motor or sensory disability, an acute relapse and/or corticosteroid pulse in the previous four weeks of assessment. Healthy controls were required to score above 26 points on the Folstein Mini-Mental State Examination (MMSE) (Butman et al., 2001) and less than 14 on the BDI-II (Beck, Steer, & Brown, 2006) and have no history of neurological disease. The BICAMS Spanish translation was administered to all participants and at follow-up as well as the MS Functional Composite (MSFC) (Fischer, Rudick & Cutter, 1999), Paced Auditory Serial Addition Test (PASAT) (Cutter et al., 1999) and Expanded Disability Status Score (Kurtzke, 1983). The individuals with MS performed significantly worse than the HC group on the three neuropsychological tests, included the BICAMS. Test re-test reliability was found to be excellent.

Vanotti et al. (2017)

The aim of this study was to examine performance on the BICAMS compared to clinical characteristics, perceived cognitive difficulties and key employment variables. The same sample of fifty participants as the other Vanotti paper with MS were recruited for the study and the inclusion criteria for these has been described above. Diagnosis was made according to the revised McDonald criteria (Polman et al.,

2011). Participants completed the BICAMS Spanish translation, the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ)(Benedict et al., 2004), the Expanded Disability Status Score (EDSS) (Kurtzke, 1983), the Paced Auditory Serial Addition Test (PASAT) (Cutter et al., 1999), the Beck Depression Inventory (BDI-II) (Beck et al., 2006) and the Fatigue Severity Scale (FSS) (Krupp, Alvarez, LaRocca, & Scheinberg, 1988). The results showed that disease progression and employment were most strongly correlated with cognitive performance on the BICAMS test. Gender, years of education and patient reported cognitive status were not found to be predictive of cognitive performance.

Walker et al. (2016)

The objective of the study was to validate the BICAMS in a Canadian population and to examine if self-reported cognition predicted vocational status. Fifty-seven individuals with MS were recruited from the Ottawa Hospital for MS. Fifty-one healthy controls were recruited from the community or were friends or family members (not first degree relative) and were matched on age, gender and education. Exclusion criteria included any neurological, medical, or psychiatric conditions including head trauma, developmental difficulty, a history of seizures, uncorrected visual acuity problems, corticosteroid or immunosuppressive treatment within two months of inclusion in the study, a current MS relapse and a history of drug dependence. Participants completed the BICAMS battery and at follow-up, as well as the Patient Health Questionnaire (PHQ-9) (Löwe, Unützer, Callahan, Perkins,

& Kroenke, 2004). The results showed that adults with MS had significantly higher levels of depression and fatigue. Participants with MS performed significantly worse than healthy controls at baseline and at follow-up according to the SDMT and the BVMT-R. However no group differences were observed in CVLT-II performance between the groups after accounting for the effects of depression and fatigue. Over half of the sample were identified to have a cognitive impairment (57.9%). The BICAMS had good test-retest reliability, especially with scores on the SDMT. There was no statistically significant association between the BICAMS variables and subjective cognition. The only BICAMS subscale found to reliably predicted employment to a significant degree was the BVMT-R.

2.4.12. Meta-Analysis of BICAMS validation studies

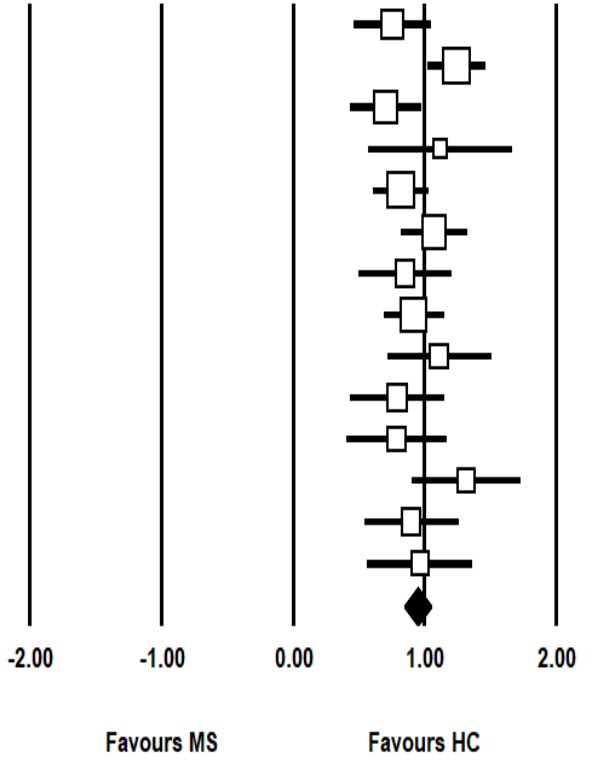
The results from all three subscales of the BICAMS, which are SDMT, CVLT-II and BVMT-R, showed that adults with MS performed significantly worse than controls across all three cognitive domains.

2.4.13. Symbols Digit Modalities Test (SDMT)

The forest plot presented in Figure 2 shows the effect size for each study which tested the SDMT in MS cases and controls. The analysis showed that overall information processing speed was significantly reduced in adults with MS compared to HC, with a large effect size ($g = 0.943$, 95% CI = 0.839, 1.046, $p < .001$). The

sensitivity analyses found no evidence of outliers, heterogeneity ($Q = 20.66$, $p > .05$) or publication bias present (Egger's test = $p > .050$, 2-tailed). The associated funnel plot (see Appendix) shows that the effect sizes were symmetrical. As a result the trim and fill analysis (Duval & Tweedie, 2000) estimated that there were 0 missing studies from the analysis.

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Costers (2017)	0.755	0.148	0.022	0.465	1.045	5.100	0.000
Dusankova (2012)	1.241	0.108	0.012	1.029	1.453	11.487	0.000
Eshaghi (2012)	0.703	0.136	0.018	0.437	0.969	5.179	0.000
Giedraitiene (2015)	1.118	0.278	0.077	0.572	1.663	4.018	0.000
Niccolai (2015)	0.819	0.105	0.011	0.614	1.025	7.804	0.000
Niino (in press)	1.071	0.128	0.016	0.821	1.321	8.388	0.000
O'Connell (2015)	0.850	0.180	0.032	0.497	1.203	4.718	0.000
Ozakbas (2017)	0.918	0.116	0.014	0.690	1.146	7.886	0.000
Polychroniadou (2016)	1.110	0.200	0.040	0.718	1.501	5.551	0.000
Sandi (2015)	0.793	0.181	0.033	0.438	1.148	4.376	0.000
Spedo (2015)	0.788	0.192	0.037	0.412	1.163	4.111	0.000
Strober (2009)	1.314	0.211	0.044	0.901	1.727	6.238	0.000
Vanotti (2016)	0.898	0.180	0.032	0.545	1.251	4.991	0.000
Walker (2016)	0.963	0.202	0.041	0.566	1.359	4.760	0.000
	0.943	0.053	0.003	0.839	1.046	17.850	< 0.001



Note. Healthy Control (HC); Multiple Sclerosis (MS).

Figure 2. Forest plot for the Symbol Digit Modalities Test (SDMT).

2.4.14. California Verbal Learning Trials (CVLT-II)

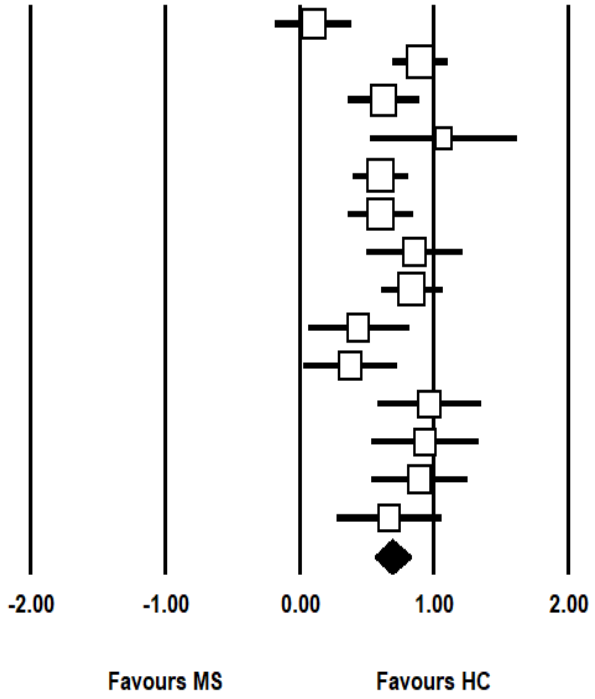
Figure 3 displays the forest plot of effect sizes for each study which compared CVLT-II performance between MS cases and controls. Overall immediate verbal recall was significantly lower in individuals with MS compared to HC, with a medium effect size (g = 0.688, 95% CI = 0.554, 0.822, p < .001). The sensitivity analyses showed that while there was no evidence of outliers, heterogeneity was indicated (Q = 36.04, p < .001) to a moderate extent (I^2 = 63.94). The Trim and Fill method indicated that only one study would be required to fall on the left of the mean effect size to make the plot symmetrical (see Appendix). Therefore, with the addition of the single imputed study, the adjusted effect size remained medium (g = 0.671, 95% CI = 0.539, 0.804). Egger's test was non-significant (p = .750, 2-tailed) indicating that there was no evidence of publication bias.

2.4.15. Brief Visual Memory Test Revised (BVMT-R)

The forest plot presented in Figure 4 show the effect sizes for the studies which tested MS performance on the BVMT-R with that of HC. The meta-analysis showed that overall immediate recall of visual memory was reduced in adults with MS compared to HC, with a medium effect size (g = 0.635, 95% CI = 0.534, 0.736, p < .001). Formal sensitivity analyses showed that there was no evidence of outliers or heterogeneity (Q = 20.727, p > .05). The funnel plot presented in the Appendix demonstrates that the effect sizes were symmetrical. Thus the trim and fill analysis

estimated that there were 0 missing studies from the analysis. Egger's test ($p = .781$) indicated that there was no evidence of publication bias.

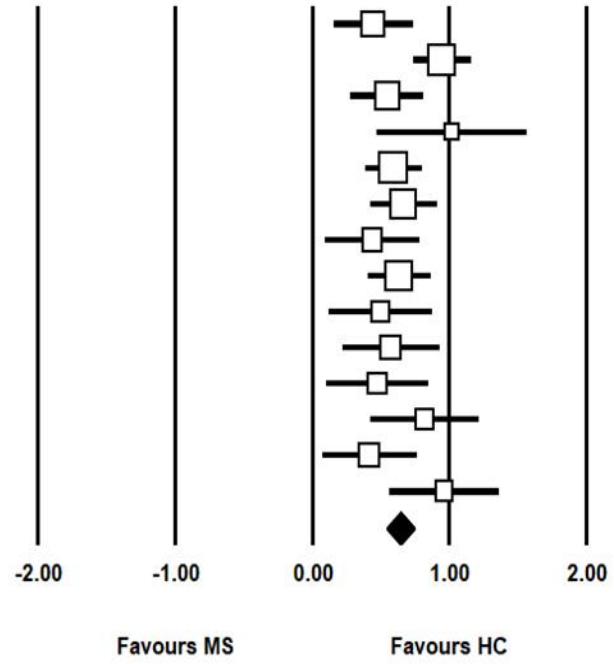
Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Costers (2017)	0.105	0.143	0.020	-0.176	0.385	0.732	0.464
Dusankova (2012)	0.898	0.105	0.011	0.693	1.103	8.584	0.000
Eshaghi (2012)	0.623	0.135	0.018	0.358	0.887	4.617	0.000
Giedraitiene (2015)	1.072	0.277	0.077	0.529	1.614	3.870	0.000
Niccolai (2015)	0.601	0.103	0.011	0.399	0.803	5.827	0.000
Niino (in press)	0.605	0.122	0.015	0.365	0.844	4.951	0.000
O'Connell (2015)	0.853	0.180	0.032	0.500	1.207	4.736	0.000
Ozakbas (2017)	0.837	0.115	0.013	0.610	1.063	7.246	0.000
Polychroniadou (2016)	0.440	0.189	0.036	0.069	0.810	2.327	0.020
Sandi (2015)	0.380	0.176	0.031	0.035	0.725	2.159	0.031
Spedo (2015)	0.965	0.195	0.038	0.583	1.348	4.949	0.000
Strober (2009)	0.935	0.201	0.041	0.540	1.329	4.642	0.000
Vanotti (2016)	0.890	0.180	0.032	0.538	1.243	4.952	0.000
Walker (2016)	0.664	0.197	0.039	0.279	1.049	3.376	0.001
	0.688	0.069	0.005	0.554	0.822	10.040	0.000



Note. Healthy Controls (HC); MS (Multiple Sclerosis).

Figure 3. Forest plot for California Verbal Learning Trials II (CVLT-II).

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Costers (2017)	0.443	0.145	0.021	0.159	0.727	3.059	0.002
Dusankova (2012)	0.944	0.105	0.011	0.739	1.150	8.993	0.000
Eshaghi (2012)	0.545	0.134	0.018	0.282	0.808	4.061	0.000
Giedraitiene (2015)	1.016	0.275	0.076	0.477	1.556	3.690	0.000
Niccolai (2015)	0.591	0.103	0.011	0.389	0.793	5.735	0.000
Niino (in press)	0.663	0.123	0.015	0.423	0.904	5.407	0.000
O'Connell (2015)	0.438	0.175	0.030	0.096	0.780	2.510	0.012
Ozakbas (2017)	0.632	0.113	0.013	0.410	0.855	5.573	0.000
Polychroniadou (2016)	0.497	0.190	0.036	0.126	0.869	2.624	0.009
Sandi (2015)	0.571	0.178	0.032	0.222	0.920	3.210	0.001
Spedo (2015)	0.475	0.187	0.035	0.108	0.841	2.537	0.011
Strober (2009)	0.822	0.199	0.040	0.432	1.213	4.129	0.000
Vanotti (2016)	0.417	0.174	0.030	0.076	0.758	2.399	0.016
Walker (2016)	0.962	0.202	0.041	0.565	1.358	4.756	0.000
	0.635	0.051	0.003	0.534	0.736	12.338	< 0.001



Note. MS (Multiple Sclerosis); HC (Healthy Controls).

Figure 4. Forest plot for the Brief Visual Memory Test Revised (BVMT-R).

2.5. Discussion

2.5.1. Summary of Findings

The aim of the review was to synthesise the studies produced as part of the international validation of the BICAMS through conducting a systematic review and meta-analysis. Sixteen studies were included into the systematic review. Of those identified, 14 articles met the additional criteria to be included in a meta-analysis.

The results from the systematic review showed that the BICAMS international validation protocol had been embraced and adhered to by many different countries, as demonstrated by its broad validation across different languages, cultures and locations. The brief tool for assessing cognition in MS was applied to cases with different MS disease courses, durations and severity. Most studies reported attempts to include a matched HC group. The occupation of the BICAMS examiner was underreported in most studies; however this detail has important implications, since the BICAMS is purported to be able to be administered by most healthcare professionals.

Adults with MS consistently showed difficulties with cognition compared to the HC across three individual meta-analyses. Cognitive impairment was most prevalent in IPS, followed by immediate verbal and visual recall. This is not the first study to demonstrate that cognitive difficulties arise in MS. The results of the current review are in line with the established knowledge and view of earlier literature, which demonstrate IPS is significantly reduced in MS (Costa et al., 2016). There is an emerging evidence base focused on the profile of cognitive impairment in MS.

Recent taxonomies have been proposed, which categorise ~7% of individuals with MS with impaired IPS, ~18% with memory impairment, ~17% with IPS and memory impairment, while the remaining 50% are not cognitively impaired (Leavitt, Tosto, & Riley, 2018). The current meta-analysis is unable to confirm the suggested taxonomies. However from the results there is a strong argument for IPS being the primary cognitive deficit in MS. This current review adds to the existing reviews which have shown differences in cognition between people with MS and controls in a number of ways. Firstly it allows for comparison of performance between individuals from the same country, as opposed to US norms (Benedict et al., 2012). Secondly it evaluates a standardised tool which assesses the three most prevalent areas of cognitive impairment which were decided by an expert consensus. Thirdly the inclusion of the meta-analysis was able to investigate consistency in cognitive performance across the validation studies.

2.5.2. Beyond validation studies

BICAMS has been investigated beyond the validation studies. While the primary focus of this systematic review was on those articles within the international protocol, it is important to recognise the wider context. Studies outside the international validation examine how BICAMS relates to personal factors, brain structure and treatments. Several socio-demographic and health factors were related to at least one impairment on a BICAMS subscale. They included older age, lower education, higher EDSS and male gender (Sacca et al., 2016). An MRI study

showed that low brain parenchymal fraction (BPF) and high T2 lesion volume (T2-LV) were associated with cognitive impairment on the BICAMS (Uher et al., 2017).

BICAMS has been applied to examine the impact of a range of treatments. Remote telephone assessment of the CVLT-II was found to yield similar results to in person administration (Barcellos et al., 2017). Visuospatial memory improved in people with MS who took betula papyrifera, a resinous extract, twice daily (Sedighi, Pardakhty, Kamali, Shafiee, & Hasani, 2014). Performance on the SDMT subscale of the BICAMS improved greatly over a six week home-based computerised assessment (Campbell, Langdon, Cercignani, & Rashid, 2016). The BICAMS battery was used to explore the efficacy of DMDs (Cinar, Kösehasanoğulları, Yigit, & Ozakbas, 2017).

2.5.3. Impact on quality of life

Cognitive impairment has a major negative impact on quality of life, including financial situation, which is independent of physical disability (Kavaliunas et al., 2017). Better BICAMS performance is related to more independent activities of daily living (Goverover, Chiaravalloti, & DeLuca, 2016). BICAMS is significantly correlated with the Expanded Disability Status Scale (EDSS), which measures MS disability (Kurtzke, 1983). The SDMT is a strong predictor of functional decline in work status (Benedict et al., 2016) and unemployment (Campbell, Rashid, Cercignani, & Langdon, 2016). Impaired SDMT, in particular, predicts poor health related quality of life (Hoogs, Kaur, Smerbeck, Weinstock-Guttman, & Benedict, 2011) and also impacts on

caregivers' quality of life (Labiano-Fontcuberta, Mitchell, Moreno-García, & Benito-León, 2014).

2.5.4. Strengths

The current review has a number of strengths to highlight, particularly related to the acceptability and feasibility of the BICAMS. The countries which participated in the international validation protocol agreed that the BICAMS could be administered and completed easily in under 15 minutes with minimal materials. There was a wide representation of cultures, languages and locations involved in the international protocol initiative. This has been quantified by comparison of the sample sizes per study against the number of those reported with MS in each country according to the Atlas of MS tool (Browne et al., 2014). The greatest representation of adults with MS in the current review was from Lithuania.

The BICAMS was validated within three English speaking countries as part of the international validation protocol (USA, Canada and Ireland). It is important to note here the necessity of this undertaking, as there is a distinction between language and culture. The cultural norms of these specific populations are markedly different and this is likely to interfere with the reliability of cognitive testing (e.g. Chevalier, Stewart, Nelson, McInerney, & Brodie, 2016). Further nationality significantly predicts performance all BICAMS subscales, even after adjusting for age and years of education (Smerbeck et al., 2017). The gender ratio observed in validation studies

are in line with the disease representation. MS disproportionally impacts more women than men (Boström & Landtblom, 2015).

This review is a significant first step in accumulating objective scores of cognitive ability in individuals with MS compared to matched HC in a brief, standardised manner. The direction of the results was as expected, as indicated by previous research studies on all three scales. It is important to consider that the CVLT-II scores were more heterogeneous than other subscales, possibly relating to the extra linguistic and cultural demands of the stimuli. This is important as cultural norms of populations are markedly different (e.g. Chevalier et al., 2016). The SDMT (infomraiton processing speed) and BVMT-R (immediate visual recall) are less linguistically or culturally loaded compared to the CVLT-II (immediate auditory verbal recall) and thus are less likely to be influenced by translation. For example, difficulty translating the CVLT-II was reported in one validation study (Costers et al., 2017). This is demonstrated in the their finding that MS cases and controls had similar scores on the CVLT-II (see Figure 3).

2.5.5. Limitations

This review has a number of limitations. Firstly, in relation to the strategy adopted. The choice of search terms may have been too constrictive, since there are additional ways to describe MS (e.g. autoimmune disorder, degenerative condition) which, if applied to the terms, could have improved the sensitivity of the search. The omission of searching reference lists and screening citing papers could have further

limited the breadth of the search, so that the number of those returned using the current strategy could have been an underestimate. The identification of three studies through expert opinion may be associated with the limitations with selectivity and sensitivity described above. It will be important for future reviews to adopt a more comprehensive search strategy after taking into consideration the points from these steps. The inclusion of Strober et al. (2009) was necessary as it includes the BICAMS subscales. Yet since it was published prior to the formal BICAMS recommendations (Langdon et al., 2012) then its design may differ from the international criteria outlined (Benedict et al., 2012). It will be important to consider this distinction when evaluating this study with others participating in the international validation process.

Secondly, in terms of sampling, there was a great deal of heterogeneity between the sample sizes and MS phenotypes. In particular this would have had an impact on the weights for each study in the meta-analysis. The disproportionate representation of each MS phenotype may have influenced the degree of the effect size, as cognitive impairment is more common in progressive forms of the disease. Thus, while RRMS was overrepresented in studies, which is consistent with prevalence rates, it may have impacted upon the effect sizes observed. The HC were recruited from the community or were related or known to the adult with MS. In the instance where HC were related to the adult with MS, then this would pose a threat to the statistical assumption of independence between the samples examined. It is important to consider the average age of those tested in the current review and that the degree of cognitive impairments identified by the BICAMS is likely to be negatively skewed,

as the range of duration of illness was over 6 years. There are issues around not controlling for the effects of comorbidity and medication on cognitive performance in the studies.

Thirdly, important relationships between cognitive impairment and moderators could not be explored in the current review. The current study was unable to perform meta-regressions to explore associations between specific cognitive impairment, disease subtype, duration, age and education. Although with future BICAMS validation studies are to be published imminently and it is likely that subsequent reviews will be able to draw more robust conclusions related to these lines of interest. Further to this point, few studies included accompanying neurocognitive assessments which examine additional cognitive domains. While it is beyond the scope of the current review to examine all aspects of cognition in MS, further investigations are required for attentional aspects, executive functioning and cognitive flexibility.

Fourthly, the quality of studies was rated relatively poorly according to the EPHPP. It is interesting to note that high quality validation studies were rated as 'Weak' on several dimensions (e.g. 'Blinding' and 'Data Collection Method'). This outcome is likely to be explained by the parameters which are usually applied to general studies not coinciding with the requirements for stringent international validation. This was evidenced by the polarity in scoring, since other dimensions were rated more strongly ('Selection Bias' and 'Study Design'). Therefore using the EPHPP to assess the quality of validation studies is likely to be unsatisfactory for this reason.

2.5.6. Recommendations

A follow-up review will be necessary once all partaking countries have published their findings. This current systematic review only provides an interim picture of the international validation of the BICAMS endeavour. Many countries have not yet published their data. Thus a subsequent review will provide a more comprehensive understanding of the international validation undertaking.

As the BICAMS is intended to be used as a screening tool to monitor cognitive ability it will be important to implement longitudinal study designs to establish scale reliability. As well as supporting understanding about cognitive profiles in RRMS and their trajectory, this may ascertain the predictive validity of the scale. BICAMS could be used alongside MRI techniques to support with the identification of biomarkers for cognitive impairment.

Understanding how the BICAMS relates to intervention for cognitive impairment is of high importance. Although clinical cut-offs have been proposed (Beier et al., 2017), there are no current thresholds for BICAMS scores. In the subsequent review it may be necessary to revisit this aspect to refine cognitive assessment. With this in mind it will be crucial to include BICAMS in research to examine efficacy of treatment.

2.5.7. Conclusions

The BICAMS has demonstrated good validity to measure cognition in MS at an international standard. It is able to distinguish cognitive impairment in individuals

with MS compared to controls across a variety of cultures, languages and locations. The international MS community has participated in the international validation protocol to great success. This is an important step in optimisation of cognitive assessment and supports with its inclusion into routine clinical appointments. The MS community has acknowledged cognitive impairment in MS as a significant issue. Studies underway which are yet to be published are expected to further improve the specificity of the BICAMS.

3. Empirical Study

Validation of the iPad Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)

3.1. Abstract

Half of those with multiple sclerosis (MS) will experience cognitive impairment. The Brief Cognitive Assessment for Multiple Sclerosis (BICAMS) was designed to assess the three most common cognitive impairments. iPad BICAMS was developed in early 2018 and could offer the added benefits of automated presentation times and scoring.

The aim of the study is to confirm the level of agreement between the iPad BICAMS and the paper and pencil form. Forty people with MS (27 females, mean age: 45, 32 RRMS) completed the following battery: (a) cognition was tested using the iPad and paper BICAMS (Symbol Digit Modalities Test, SDMT; California Verbal Learning Trials II, CVLT-II; Brief Verbal Memory Test Revised, BVMT-R); (b) premorbid functioning was assessed using the Test of Premorbid Functioning (TOPF); (c) dexterity was tested using the Nine Hole Peg Test (9HPT) and the Grooved Peg Test (GPT); (d) visual functioning was examined using the Multiple Sclerosis Vision Test Batter (MSVTB); (e) mood and anxiety was tested using the Hospital Anxiety and Depression Scale (HADS); (f) fatigue was assessed using the Fatigue Severity Scale (FSS) and; (g) a short survey captured participants' experience of BICAMS.

The iPad BICAMS showed above satisfactory level of agreement across three intraclass correlations, particularly so for SDMT (.85, 95% CI (0.74, 0.92), $p < .001$), followed by BVMT-R (.67, 95% CI (0.45, 0.62), $p < .001$) and CVLT-II (.57, 95% CI (0.32, 0.75), $p < .001$). 9HPT, GPT, HADS and high contrast visual acuity were within the mild ranges. Low contrast visual acuity and letter contrast sensitivity was in the impaired range. There were no associations found between iPad BICAMS performance and TOPF, 9-HPT or FSS. However, SDMT was found to negatively correlate with motor planning ($r = -.469$, $p = .002$) and BVMT-R with high contrast visual acuity ($r = -.459$, $p = .003$). Seventy percent of participants reported that they would be 'moderately' to 'very' satisfied to be tested by the iPad BICAMS on a yearly basis in the future.

3.2. Introduction

3.2.1. Multiple Sclerosis

Cognitive impairment is quite common in Multiple Sclerosis (MS) (Benedict & Zivadinov, 2011). MS is a chronic autoimmune, inflammatory neurological disease of the central nervous system. The hallmarks of the condition are axonal or neuronal loss, demyelination and astrocytic gliosis (Thompson et al., 2018). Symptoms are a consequence of these neurological changes and they include cognitive, motor, sensory, visual, bowel and bladder dysfunctions (Lassmann, 2010).

Diagnosis is based on the McDonald Criteria (Lublin et al., 2014). The prevalence of MS has increased greatly over the past decade (e.g. Rotstein et al., 2018). Close to 127, 000 individuals in the United Kingdom have the condition (Mackenzie, Morant, Bloomfield, MacDonald, & O'Riordan, 2014). MS is one of the most common causes of neurological disability amongst young adults (Deloire, Ruet, Hamel, Bonnet, & Brochet, 2010; Ruet et al., 2013). There are higher rates of MS in women than in men (e.g. Westerlind et al., 2014).

3.2.2. Phenotypes

Four MS individual disease courses have been distinguished (Achiron et al., 2012; Thompson et al., 2018):

(a) Relapsing Remitting MS (RRMS): The most common form of MS includes at least one episode, which involves the optic nerve, brainstem or spinal cord;

(b) Secondary-Progressive MS (SPMS): Between 15%-30% of individuals with RRMS will develop progressive disability, with or without superimposed relapses;

(c) Primary Progressive MS (PPMS): Approximately 15% of people with MS experience a progressive form of MS from the outset;

(d) Benign MS: Occurs in approximately 15% of individuals and until recently the disease course was not thought to involve significant neurological disability.

3.2.3. Cognitive Impairment in Multiple Sclerosis

Approximately 50% of people with MS have a cognitive impairment (Benedict & Zivadinov, 2011). It occurs across all phenotypes (Potagas et al., 2008). Cognitive impairment has been observed in older adulthood (Bollaert et al., 2017). It is most prevalent in progressive forms of the condition, however (Papathanasiou et al., 2014). This is evident even after a decade of illness duration (Planche, Gibelin, Cregut, Pereira, & Clavelou, 2016). Cognitive impairment has been observed across several cognitive domains.

3.2.4. Information Processing Speed (IPS) in Multiple Sclerosis

Information Processing Speed (IPS) refers to the amount of time required to process a set amount of information (Kalmar & Chiaravalloti, 2007). Prevalence rates of IPS impairments in MS is high and ranges between 20% – 50% (Grzegorski & Losy, 2017). Thus IPS is thought to represent the core cognitive difficulty in MS (Denney et al., 2004), as it occurs simultaneously with impairments in other cognitive domains (Chiaravalloti & DeLuca, 2008). However, support for this argument remains tentative due to the heterogeneity of samples and study designs in the literature (Costa et al., 2016).

3.2.5. Immediate Verbal Recall in Multiple Sclerosis

Episodic memory is the second most typical cognitive dysfunction in MS, with estimated prevalence falling between 33% – 65% (Grzegorski & Losy, 2017). Two positions have emerged from the literature, surrounding whether difficulties in verbal recall relate to retrieval (e.g. Rao et al., 1984) or acquisition deficit (Demaree, Gaudino, DeLuca, & Ricker, 2000; Gaudino, Chiaravalloti, DeLuca, & Diamond, 2001). The debate continues today, as several published meta-analyses are unable to agree on a common understanding (Lafosse et al., 2013; Prakash et al., 2008; Thornton & Raz, 1997; Wishart & Sharpe, 1997; Zakzanis, 2000).

3.2.6. Immediate Visual Recall in Multiple Sclerosis

Immediate visuospatial recall is defined as the recognition of visual information and the ability to evaluate that information (Chiaravalloti & DeLuca, 2008). This is thought to be the third most common cognitive impairment in MS (20% - 26%) (Vleugels et al., 2000). Visuospatial ability is relatively less understood than other cognitive domains but, as expected it is associated with primary visual problems. These difficulties could influence higher-order visual functions (Bruce et al., 2007). Visuoperceptual skills correlates with overall cognitive status and physical disability in MS (Vleugels et al., 2000).

3.2.7. Other cognitive impairments in Multiple Sclerosis

Attention, which refers to alertness and vigilance (Winkelmann, Engel, Apel, & Zettl, 2007), is also impaired in MS. Prevalence estimates range between 12% – 25% (Grzegorski & Losy, 2017). Difficulties have been demonstrated across many different attentional paradigms (Adler & Lembach, 2015; Beatty et al., 1995; McCarthy et al., 2005). Executive function is defined as a combination of processes required for goal-directed behaviour (Chiaravalloti & DeLuca, 2008). Executive functioning skills are impaired in MS (Santiago et al., 2007). The prevalence rates of executive functioning difficulties have been reported between 7% - 19% (Grzegorski & Losy, 2017).

3.2.8. The impact of cognitive impairment in Multiple Sclerosis

Most people with MS in the United Kingdom report experiencing cognitive impairment (72%) (Thompson et al., 2017). It is important to assess cognitive impairment as the literature suggests that it negatively impacts on quality of life, over and above the impact of physical impairments (Langdon, 2010). Participatory activities, including employability (Morrow et al., 2010), driving (Lincoln & Radford, 2008) and leisure activities (Patel, Walker, & Feinstein, 2017) are all adversely influenced by cognitive impairment. Cognitive impairment also increases risk for falls (Gunn et al., 2013) and issues with drug adherence (Bruce et al., 2010).

3.2.9. Therapeutic interventions in Multiple Sclerosis

A variety of disease modifying dugs (DMD) ameliorate MS symptoms (Tsivgoulis et al., 2015), however at present there are none available to specifically target cognitive impairment (Benedict & Zivadinov, 2011). Specific cognitive training and holistic approaches are available to improve cognitive ability (Charvet et al., 2017; Mattioli et al., 2016). There is strong evidence to show that cognitive rehabilitation is effective up to six months following intervention (Chiaravalloti, Moore, Nikelshpur, & DeLuca, 2013). Thus cognitive assessment is vital to guide referral for targeted intervention.

3.2.10. Assessing cognition in Multiple Sclerosis

There are no diagnostic criteria for cognitive impairment in MS (Thompson et al., 2017). Until recently cognitive assessments were typically conducted exclusively in University Hospitals and Specialist MS Centres. Assessment can be challenging in clinical contexts for numerous reasons: firstly (a) Magnetic Resonance Imaging (MRI) is not precise enough to assess cognitive impairment (Rocca et al., 2015); secondly (b) clinical interview and standard neurological examination are not sufficiently sensitive to identify impairment in MS (Romero et al., 2015); and thirdly (c) self-reported cognitive complaints are obscured by mood and other subjective symptoms (Carone, Benedict, Munschauer, Fishman, & Weinstock-Guttman, 2005). Thus, objective assessments of performance are needed.

3.2.11. Neuropsychological assessments in Multiple Sclerosis

Neuropsychological assessments contain standardised instructions, scoring criteria, normative data and psychometric properties and can be applied to assess a range of cognitive domains, including language, visual processing, memory, IPS, cognitive flexibility and executive functioning (Lezak, 1995). Cognitive domains such as IPS and anterograde episodic memory can be difficult to assess without neuropsychological testing (Rao, St Aubin-Faubert, & Leo, 1989).

Several brief assessments are available to screen for cognitive impairment in MS (e.g. Freitas et al., 2016; Hansen et al., 2015; Hansen et al., 2017). Yet they differ in their focus of assessment and definition of clinical thresholds for impairment. MS-specific neuropsychological test batteries are sensitive to assess for cognitive impairment in the condition (e.g. Gromisch et al., 2016). The most commonly used of these is the Brief Repeatable Battery of Neuropsychological Tests (BRB) (Rao & Group, 1990) which takes approximately 45 minutes to administer. The BRB includes the Selective Reminding Test (verbal memory), the Symbol Digit Modality Task (SDMT; IPS), the Paced Auditory Serial Addition Test (PASAT; IPS), the 10/36 Spatial Memory Test, and Verbal Fluency (executive skills).

The Minimal Assessment of Cognitive Function in MS (MACFIMS) (Benedict et al., 2002; Guimarães & Maria José Sá, 2012) is a more comprehensive assessment of cognition in MS. MACFIMS takes 90 minutes to administer and includes SDMT for IPS, PASAT for IPS, D-KEFS Sorting Task (executive skills – flexibility), CVLT-II for verbal memory, BVMT-R for visual memory, Controlled Oral Word Association Test (COWAT) for language and the Judgement of Line Orientation (JLO) for spatial skills.

3.2.12. Brief International Cognitive Assessment for Multiple Sclerosis

There are several caveats to using neuropsychological batteries, which includes access resources and specialist training needs (e.g. Santos, Pinheiro & Barros, 2015). The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) (Langdon et al., 2012) was developed in 2010 as a brief screen of cognitive

impairment for small centres with limited neuropsychological expertise. The BICAMS includes the (a) Symbol Digit Modalities Test (SDMT; (Smith, 1982); (b) California Verbal Learning Test II (CVLT-II; (Delis, 2000) learning trials; and (c) Brief Visual Memory Test - Revised (BVMT-R; Benedict, 1997) learning trials, which assess domains of IPS, immediate verbal and visual recall.

The BICAMS assesses the most prevalent cognitive impairments in MS, which occur at any stage of the disease and within all phenotypes. BICAMS could be used to determine the predictive value of subsequent cognitive functioning (Bergendal, Fredrikson, & Almkvist, 2007) as well as monitoring DMD treatment (Cinar et al., 2017). Several validation studies have been published and are underway as part of the international validation protocol.

3.2.13. Computerised neuropsychological assessments

Computerised cognitive batteries may overcome the difficulties with conventional assessment, including stimuli display times and automated scoring (Lapshin, Oconnor, Lanctt, & Feinstein, 2012). iPad BICAMS is arguably the next step in cognitive assessment in MS. The physical (visual and auditory) parameters of the tests have been kept constant with the paper version. iPad BICAMS runs on two iPads, with individual software for the examiner and the participant versions. The written instructions for the investigator have been amended from the paper manual to accommodate the iPad format. The iPad BICAMS improves validity and efficiency of testing by evaluating whether the participant has sufficient visual acuity and

manual dexterity to proceed with the exam, controlling exposure time of BVMT-R and automatic scoring of SDMT and CVLT-II trials. As well as meeting patient expectations, making iPad BICAMS scores digital is necessary to coincide with Electronic Health Records (EHR).

Cognitive assessments for iPads have been developed and validated in other neurodegenerative conditions. For example the Cognitive Assessment for Dementia (CADi) has been validated in individuals with dementia with acceptable Cronbach's alpha values (over 0.7) and test-retest reliability at one-year (Onoda et al., 2013). Similarly the Computerized Cognitive Composite for Preclinical Alzheimer's Disease (C3-PAD) has shown excellent validity (0.93) compared to home versus clinic cognitive performance (Rentz et al., 2016).

3.2.14. Factors associated with cognitive ability

There are various methods of assessing cognition in MS, which have been described above. When evaluating cognitive ability it is important to consider wider contextual interpretations, which might be associated with scores (Lezak, Howieson, Lorin & Fischer, 2004). This is crucial since MS is particularly heterogeneous (Disanto et al., 2011). These personal factors could contribute in some way with cognitive performance, including those which have been outlined in the literature below.

3.2.15. Mood and anxiety

Depression and anxiety are the most commonly experienced mental health problems in MS (Turner et al., 2016). These factors have been shown to impact on objective cognitive performance in MS (Nunnari et al., 2015), in areas such as IPS, visual-spatial memory and executive functioning (Morrow, Rosehart, & Pantazopoulos, 2015).

3.2.16. Fatigue

Fatigue is extremely common in MS (50% - 90%) and negatively impacts on quality of life and employability (Amato et al., 2001; Flensner, Landtblom, Söderhamn, & Ek, 2013). Fatigue impairs task endurance (Sandry, Genova, Dobryakova, DeLuca, & Wylie, 2014) and interferes with many aspects of cognitive performance, including speed of visual processing (Kluckow, Rehbein, Schwab, Witte, & Bublak, 2016), memory, visuomotor abilities and attention (Pokryszko-Dragan et al., 2016).

3.2.17. Dexterity

Most people with MS experience upper limb dysfunction, which leads to increased dependency and negatively impacts on quality of life (Lamers & Feys, 2014) and employment (Marrie et al., 2017). There are a variety of tools to assesses dexterity in MS, which include the Nine Hole Peg Test (9-HPT) and the Grooved Peg Test (GPT). These tests differ in their sensorimotor assessment, in particular the GPT is more complex and requires a higher level of motor planning demands than the 9-HPT.

3.2.18. Visual Functioning

Problems with vision are a common manifestation in MS due to incomplete recovery from optic neuritis (ON) or impairment to the optic pathway occurring independently from ON (Oberwahrenbrock et al., 2012). A recent review demonstrated that high-contrast visual acuity (HCVA) remains functional in MS, but Low-Contrast Letter Acuity (LCLA) is impaired (Balcer et al., 2017). As might be expected, a correlation has been reported between LCLA and the Expanded Disability Status Score (EDSS) (Balcer et al., 2003), which is the gold standard for measuring MS disability (Kurtzke, 1983).

3.2.19. Premorbid functioning

Cognitive reserve is an important predictor of better performance on cognitive tests in individuals with MS (Chillemi et al., 2015; Modica et al., 2016; Nunnari et al., 2016). In particular, a review highlighted that high premorbid intelligence improves neuropsychological functioning (Benedict & Zivadinov, 2011). High levels of education plays a protective role in MS with a short rather than long duration (Rimkus et al., 2018).

3.2.20. Summary

Cognitive assessment is central to the management of MS. There are several means of assessing cognition, which include MRI, patient report or neuropsychological

batteries. Traditional neuropsychological batteries are sensitive to cognitive impairment and offer an objective measure of performance compared to alternative methods. Yet they are lengthy and require specialist training and materials. The BICAMS can be completed in under 15 minutes and assesses the three most prevalent cognitive impairments in MS, using only paper, a pencil and a stopwatch. The recently developed iPad BICAMS is expected to offer the same benefits in assessment as the paper and pencil version, with the added assistance of automated display times and scoring. In addition to the need of a precise and time effective measurement of cognition, contextual factors are important when evaluating performance, particularly when MS is heterogeneous (Disanto et al., 2011). The objective of this study will be to confirm that the iPad BICAMS reaches the same level of agreement as the paper and pencil version and that patient satisfaction will be greater for the iPad version compared to the conventional form.

3.2.21. Aim

The main aim of the study will be to examine the level of agreement between the iPad and the paper version of the BICAMS in adults with MS, explore related factors which might influence cognition and investigate participant satisfaction with being tested by the iPad.

3.2.22. Hypotheses

First Hypothesis

There will be a high level of agreement between the iPad and paper BICAMS.

Second Hypothesis

There will be a negative association between performance on iPad BICAMS and mood, fatigue, visual functioning and dexterity. In addition there will be a positive association between premorbid intellectual ability and cognitive ability on the BICAMS.

Third Hypothesis

Participants will report that they perceive being tested by the iPad BICAMS as being more easy and enjoyable than the paper version.

3.3. Method

3.3.1. Research Approval

The project received a favourable ethical opinion from the North East - Tyne & Wear South Research Ethics Committee following submission to a Proportionate Review Authority (ref: 17/NE/0352; see Appendix). The study was certified by the Research Ethics Committee at Royal Holloway, University of London.

3.3.2. Sample and setting

Inclusion and Exclusion Criteria

The inclusion criteria:

(a) Diagnosis of MS by a Consultant Neurologist based on Polman et al. (2011) or equivalent
(b) Aged between 18 – 65 years
(c) Born and educated in England
(d) Able to give informed consent

The exclusion criteria:

(a) Any other primary neurologic or psychiatric condition that might separately contribute to cognitive impairment.
(b) A sensorimotor impairment that would confound the testing performance.

The study took place within the Neurology department of the Royal London Hospital or at participant's homes. The Clinical Trials Coordinator identified participants. Participants who had given consent to be contacted for research purposes were invited to take part in the study via email or were given the Information Sheet when they attended clinic appointments. No information was collected about response rate.

3.3.3. Materials and measures

3.3.4. Premorbid Functioning

The Test of Premorbid Functioning (TOPF) (Wechsler, 2011) eliminates premorbid intellectual functioning for individuals aged between 16-90 (see Appendix). Participants are instructed to read a list of up to 70 English words out loud. The words have atypical grapheme to phoneme translations. The number of correct responses are used in a calculation, in addition to the participant's gender, age and years of education, to provide an overall premorbid full-scale intelligence quotient (Wechsler, 2011). According to the scale, scores are considered in the following ranges: 80 to 89 'low average'; 90 to 110 'average'; 110 to 119 'high average'; 120 to 129 'superior'. The TOPF shows good test re-test reliability (r =.89 to .95) and high split-half reliability (r = .92 to r = .99) (Wechsler, 2011) and it has been utilised previously to assess premorbid function in MS (Berg, Durant, Banks, & Miller, 2016).

3.3.5. Cognition

3.3.6. Brief International Cognitive Assessment for Multiple Sclerosis

The BICAMS (Langdon et al., 2012) consists of three subtests (see Appendix) which assess the following areas of cognition:

The Symbol Digit Modalities Test (SDMT) assesses IPS (Smith, 1982). At the top of the SDMT record form is a nine-item key which contains symbols which are paired with numbers. The examiner instructs the participant to vocalise as quickly as possible the

numbers which correspond with the symbols presented in the empty boxes on the record sheet within a 90-second limit. The score is obtained by calculating the total sum of the correct responses.

The SDMT-oral demonstrates excellent psychometric properties (Jaywant, Barredo, Ahern & Resnik, 2016), including test retest reliability (r = .80) (Smith, 1982) and moderate to high concurrent validity (correlations with WAIS Digit Symbol Coding subtest of r = .62 to r = .91) (Bowler, Sudia, Mergler, Harrison & Cone, 1992; Hinton-Bayre, Geffen, & McFarland, 1997; Lewandowski, 1984; Morgan & Wheelock, 1992). The psychometric properties remain high in MS populations, the SDMT has good construct validity (Christodoulou et al., 2003), sensitivity (78-82%) and specificity (60-69%) to cognitive impairment (López-Góngora et al., 2015; Parmenter et al., 2007) and it can distinguish adults with MS from healthy controls (HC) (Drake, Weinstock-Guttman, Morrow, Hojnacki, Munschauer & Benedict, 2010; Hughes et al., 2011; Langdon et al., 2012; O'Connell et al., 2015).

The California Verbal Learning Test II (CVLT-II) learning trials (Delis, Kramer, Kaplan & Ober, 2000) examines immediate verbal recall. The CVLT-II consists of a 16-item list of English words. The experimenter reads aloud the list at a rate of slightly slower that one word per second and the participant is asked to respond immediately once the last word has been read with as many words as they can remember in any order. The overall score is derived from the total sum of correct responses over the five trials.

The complete CVLT-II shows good psychometric properties yet these should be interpreted inferentially as only the first five learning trials appear in the BICAMS (Langdon et al., 2012). In MS samples the CVLT-II shows good sensitivity (61%; (Niccolai et al., 2015) and sensitivity to detect cognitive impairment (Strober et al., 2009). In addition the CVLT-II has good test retest reliability (Benedict, 2005; Delis, Kramer, Kaplan & Ober, 2000).

The Brief Visual Memory Test - Revised (BVMT-R) learning trials (Benedict, 1997) assesses immediate visual recall through the presentation of 2 x 3 geometric figures. These figures are displayed for 10 seconds before being removed from view for a total of three trials. The examiner instructs participants to draw these shapes accurately and in the same position as had been located on the stimulus sheet. Scores are assigned to the BVMT-R for accuracy and precision position on the matrix with a maximum possible score of 36.

The BVMT-R has good psychometric properties, including good inter-rater reliability ($r > .90$), and good test-retest reliability ($r = .80$) (Benedict, 1997), although they should be considered as inferential as only the learning trials were conducted (Langdon et al., 2012). The test shows good sensitivity to cognitive impairment in MS (60) (Benedict et al., 2001; Langdon et al., 2012; Niccolai et al., 2015) and concurrent validity correlates strongly with measures of explicit memory ($r= .65$ to $.80$) (Benedict, 1997).

3.3.7. iPad BICAMS

iPad BICAMS was developed using REACT.JS and REDUX frameworks and operates on a pair of Apple iPads. There is an examiner and participant version. The parameters of the iPad version are consistent with the original paper form, apart from the written instructions which have been amended to accommodate the iPad format. The web application securely, and in an anonymous form, automatically submits results to a centralised database on the bicams.net website using .NET MVC backend to provide secure Application Processing Interfaces (API) to retrieve and save processed data. The application automatically scores performance on the SDMT and CVLT-II while BVMT-R drawings are saved to be scored later by the examiner.

3.3.8 Associated Factors

3.3.9. Depression and anxiety

The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) contains 14-items which assess depression and anxiety symptoms separated into two subscales (see Appendix). Each item is rated from 0-3, with higher ratings indicating higher symptom severity. Cut-offs of 0-7 (normal range), 8-10 (mild range), 11- 14 (moderate range), 15-21 (severe range) have been recommended (Zigmond & Snaith, 1983). The scale has been validated for use in individuals with MS (Honarmand & Feinstein, 2009) and has been demonstrated to be more effective than the Beck Depression Inventory-Fast Screen (BDI-FS) at predicting functional outcomes in those with depression (Hanna et al., 2017). The anxiety and depression

subscales have been found to show good internal consistency (α = .82 and .83 respectively) (Honarmand & Feinstein, 2009). Caseness for anxiety and depression has been reported at 8/21 with a specificity of 78% and sensitivity of 90% for anxiety, and a specificity of 79% and sensitivity of 83% for depression (Bjelland, Dahl, Haug, & Neckelmann, 2002). The scale has been shown to be sensitive to depression and anxiety in MS (Watson, Ford, Worthington, & Lincoln, 2014). A reliability analysis showed that showed the HADS-A and HADS-D reached acceptable reliability rates respectively (α = 0.82; α = 0.75).

3.3.10. Fatigue

The Fatigue Severity Scale (FSS) (Krupp et al., 1989) contains 9-items which assess the impact of fatigue on functioning over the previous week (e.g. motivation, physical functioning, employment) on a 7-point Likert scale (see Appendix). The sum of the total score is used to indicate overall fatigue, with a clinical-cut off for individuals with MS set at scores of 36 and above to demonstrate severe fatigue (Krupp et al., 1989). The FSS has been shown to demonstrate excellent internal consistency (α = .81) for people with MS and good test-retest reliability (Krupp et al., 1989). The instrument demonstrates moderate test re-test reliability over six months and adequate construct validity (Learmonth et al., 2013) and for discriminate use in MS populations (Flachenecker et al., 2002). Cronbach's alpha showed the FSS questionnaire to reach acceptable reliability, α =0.91.

3.3.11. Visual Function

The Multiple Sclerosis Vision Test Battery (MSVTS) (Bullimore, 2016) contains vision tests, including HCVA, LCVA (at 2.5% and 1.25%) and Letter Contrast Sensitivity (LCS). These tests are logMAR visual acuity charts which are based on the well validated and used Bailey-Lovie acuity charts. In the visual acuity charts, a unique combination of 5 letters are shown, across 19 rows, and the letter sizes on each row gradually decrease. In the letter contrast sensitivity series, the charts are based on the same principles as the Pelli-Robson Chart and the same 10-letter set as the Bailey-Lovie visual acuity chart. Two letters are presented together in 0.1 log unit steps and there are 23 different combinations.

The MSVTS is presented on an iPad with autobrightness set to halfway and room lights may be dimmed or left on. The MSVTS does not require external lighting. The screens were visually assessed for reflections which could obscure the letters and repositioned if necessary. Participants are instructed to read aloud the letters they could see, with both eyes open, starting with those of high contrast until no letters on a given page is read correctly. Participants were encouraged to study a page for several seconds and guess the letter, even if they claim to be unable to see anything. Scoring for the visual acuity charts was based on the lowest line recorded and the Snellen fraction was calculated as the test distance divided by the lowest line. Scoring for the letter contrast sensitivity charts was recorded by each individual letter read correctly and multiplying by 0.05. The iPad-based assessment of Low-Contrast Visual Acuity shows good agreement with the superior Sloan testing in individuals with MS (Sattarnezhad, Farrow, Kimbrough, Glanz & Healy, 2017).

The ICD 10 visual impairment criteria (ICD-10 World Health Organization, 1992) were used to interpret logMAR scores for HCVA, LCVA (at 2.5% and 1.25%). A score of 0 would indicate 'normal vision'; 0.5 to 1.0 'moderate visual impairment'; 1.1 to 1.3 'severe visual impairment'; 1.4 or greater 'blindness'. For contrast sensitivity, a Pelli-Robson score of 2.0 signify normal contrast sensitivity of 100 percent. Thus scores less than 2.0 indicate poorer contrast sensitivity. A score of less than 1.5 indicates visual impairment and a score of less than 1.0 represents a visual disability (Parede, Torricelli, Mukai, Netto, & Bechara, 2013).

3.3.12. Dexterity

The Nine-Hole Peg Test (9HPT) (Mathiowetz et al., 1985) assesses dexterity (see Appendix). In the test participants are instructed to move nine pegs from the container to an empty hole, one by one, until all the holes are filled. Once all the pegs have been placed into empty holes the participant must return the pegs individually to the container. They are required to do this as quickly as possible. The other hand is required to stabilise the pegboard. The test is completed twice, once for each hand, starting with the dominant hand. Scores are calculated from the time taken to complete the task, with quicker scores indicating superior dexterity. The cut-off score of 33 seconds has been recommended to differentiate mild from severe upper limb dysfunction in people with MS (Lamers et al., 2014).

The 9HPT has been included in the MS functional composite measure (MSFC) (Fischer, Rudick, Cutter & Reingold, 1999). The 9HPT has a high inter-rater (r = .84 -

.96) and intra-rater (r = .91 - .99) reliability (Solari, Radice, Manneschi, Motti, & Montanari, 2005) as well as excellent internal consistency (α = .93; and high test-retest reliability (r = .88) (Rasova, Martinkova, Vyskotova & Sedova, 2012). Concurrent validity reported between the EDSS score and 1-year change (r = .27) (Cutter et al., 1999). The 9-HPT has been shown to reliably discriminate between individuals with MS and healthy controls (Feys et al., 2017). A poor performance on the 9HPT has been shown to be indicative of cerebellar atrophy (Ruet et al., 2014) (Van De Pavert et al., 2016). The 9HPT has been widely applied as an assessment of upper extremity tremor (Alusi, Worthington, Glickman, Findley, & Bain, 2000; Fox, Bain, Glickman, Carroll, & Zajicek, 2004).

The Grooved Pegboard Test (GPT) (Matthews & Klove, 1964) assesses higher level dexterity. There are 25 holes in the GPT, participants are instructed to precisely orient and insert canoe-shaped pegs into differently oriented canoe-shaped holes. The researcher begins by placing five pegs in the top five holes and then instructs the participant to complete the remaining 20 sequentially from the opposite side of the board to the hand that they are using, completing a line and then returning to the opposite side from the hand that they are using, until all lines are completed. This procedure is completed once for each hand (beginning with the dominant hand) and a mean score is taken.

Compared to the 9-HPT, the GPT requires more motor planning due to the nature of the orientation and insertion of the pegs. In this task there is only one correct orientation for the peg to be inserted into the hole. Since all holes are uniquely differently orientated, and thus the peg inserted must be synchronously orientated

to the hole. Scores are interpreted as lower scores indicating superior upper limb function.

The GPT shows marginal to high test-retest reliability within healthy controls (r = .67 to .86) (Dikmen, Heaton, Grant & Temkin, 1999; Levine, Miller, Becker, Selnes & Cohen, 2004; Ruff & Parker, 1993). The test has been shown to have modest concurrent validity with relation to tapping speed (Schear & Sato, 1989). GPT scores and activities of daily living in MS have been found to be weak to modestly associated (Kessler, Cohen, Lauer, & Kausch, 1991). A motor planning index (MPI) can be calculated by subtracting scores on the 9HPT from the GPT.

3.3.13. Participant's Feedback

A short 8-item survey was developed for the current study to assess participants' experience of using the BICAMS (see Appendix). Four 5-point Likert scale assessed participant's enjoyment and ease of using both BICAMS tests. A single 7-point Likert scale examined participant satisfaction at being tested by the iPad BICAMS on a yearly basis in the future. Participants were asked to state their preference of BICAMS versions. Participants were invited to provide feedback on the iPad BICAMS.

3.3.14. Experimental Design

A within-subjects cross-sectional counterbalanced randomised design was applied to compare the performance on the iPad BICAMS to the BICAMS. In other words, all

participants are exposed to each condition (iPad and paper and pencil BICAMS), the order of which has been randomised in a counterbalanced fashion, at a single time-point. The sequence of administration of the battery of assessments was randomised using the Research Randomiser version 4 (Urbaniak & Plous, 2013) to reduce systematic practice and fatigue effects.

3.3.15. Procedure

Written informed consent was gained. Participants were reminded to use eyewear to correct vision if needed on the neuropsychological test battery. Testing was carried out by a single researcher (FC, a Trainee Clinical Psychologist), following demonstration of competence at administering the battery to DL. Standardised procedures were adhered to as per individual test guidelines for the neuropsychological test battery. An iPhone application stopwatch was used for timed tasks. Testing took place in a quiet clinic room in the hospital or at participants' homes.

3.3.16. Power Analysis

A power analysis was conducted based on (Onoda et al., 2013) due to the similarity of the study design and participant sample. A one-tailed, a priori analysis of a correlation between an iPad cognitive assessment and another standardised neuropsychological test (Trail Making Test) in adults with Alzheimer's Disease was

undertaken to estimate power for the study using G*Power software (Faul et al., 2007). The power analysis specified a sample size of 55 service-users, holding an alpha at .05, with a power of .80.

3.3.17. Statistical Analysis

The data below are presented as means and standard deviations for continuous variables or proportions and frequency for categorical variables. One participant's iPad BVMT-R data's file became corrupted and so the mean value was imputed in place. Six participants were unable to discern letters presented with LCVA 1.25%.

Z-scores were produced for each variable to visually investigate for the presence of outliers. The peg test data from two participants was excluded with scores above 2 standard deviations from the mean. Histograms were generated to examine for normality, particularly considering any 'floor effects' and 'ceiling effects' of task performance. Positively skewed data according to the Shapiro-Wilk test was transformed using power transformations (2-4). This applied to the peg test data. Inverse power transformations were used to gain normality sufficient for parametric analysis for negatively skewed data. This was true for the BVMT-R scores.

Descriptive statistics were produced based on the socio-demographic and clinical characteristics of the sample (age, gender, years of education, diagnosis, duration of diagnosis, medication and mobility).

The mean scores and standard deviations of both versions of BICAMS were calculated. To examine the first hypothesis an intraclass coefficient correlation (ICC) was performed to investigate the level of agreement between BICAMS and iPad BICAMS across each subscale. ICC which are higher than .40 are commonly interpreted as evidence of scale reliability (Everitt, 2002). To examine order effects, six one way Analysis of Variance (ANOVAs) were performed. The mean and standard deviation of length of time to administer the iPad BICAMS was calculated.

A composite score for cognitive impairment was calculated based on published UK norms for the SDMT, CVLT-II learning trials and BVMT-R learning trials (Orchard, Giovannoni & Langdon, 2013). A score of 0 was assigned if a participant scored greater than or equal to the published norm. A grade of 1 was allocated if the participant scored less than one standard deviation below the mean. A score of 2 was assigned if this was less than two standard deviations below the mean. The total sum of these grades was calculated across the subscales (Camp et al., 2005).

Descriptive statistics were produced for the associated factors, which included premorbid functioning, state depression and anxiety, dexterity and visual functioning. Estimated premorbid IQ (pFSIQ) was calculated with the TOPF scorer programme (Wechsler, 2011). This calculates pFSIQ based on age, gender, TOPF raw score, and years of education. The motor planning index (MPI) was computed by subtracting the 9HPT from the GPT. To investigate the second hypothesis, a series of bivariate correlations were performed to understand the individual associations between iPad BICAMS subscales and associated variables.

To examine the third hypothesis the mean and standard deviation of ratings on the experience questionnaire were calculated. Participants' qualitative feedback was reduced into themed categories. Paired t-tests were conducted to examine differences between enjoyment and ease of BICAMS versions. Bivariate correlations were conducted to explore whether reported enjoyment and ease of testing was related to performance on the BICAMS.

The threshold for statistical significance was defined to $p < .05$. The Bonferroni correction was applied to reduce Type II error. Data was analysed using the Statistical Package of the Social Sciences (SPSS), version 24 (IBM Corporation, Armonk, NY, USA).

3.4. Results

3.4.1. Descriptive and clinical characteristics of sample

Forty individuals with MS completed the battery. An overview of the socio-demographic and clinical characteristics are presented in Table 4. Two thirds of participants were female. Participants' ages ranged between 23 and 64 years. Years of education ranged from 11 to 21. Almost half of participants were in full-time employment. Most of the participants had RRMS. The duration of illness varied greatly between 1 and 35 years. Overall mobility was fair according to the Hauser Ambulation Index.

Table 4. *Demographic and clinical characteristics of samples*

Characteristic				
Sex n (%)	Female 27 (67)	Male 13 (33)		
Age m (sd)	45 (12)			
Education m (sd)	16 (3)			
Employment n (%)	Full-time 19 (48)	Part-time 5 (12)	Unemployed 6 (15)	Other 10 (25)
Phenotype n (%)	RRMS 32 (80)	SPMS 4 (10)	PPMS 4 (10)	
Duration m (sd)	11 (10)			
Hauser Ambulation Index m (sd)	2 (3)			
Medication n (%)	Natalizumab 18 (49)	Alemtuzumab 3 (8)	Ocrelizumab 3 (8)	Other 16 (35)

Note. Mean (m); frequency count (n); Primary Progressive Multiple Sclerosis (PPMS); Relapse Remitting Multiple Sclerosis (RRMS); Secondary Progressive Multiple Sclerosis (SPMS); standard deviation (sd).

3.4.2. Associated factors

Table 5 presents the data related to premorbid functioning, mood, fatigue, dexterity and visual functioning.

3.4.3. Premorbid Functioning

The sample had above average pFSIQ, which ranged greatly from 'low average' to 'superior'. The mode was 114.

3.4.4. Depression and anxiety

The mean state depression and anxiety levels within the sample fell within the 'normal' range according to the HADS. However there were 11 cases in the clinical range for anxiety and 4 participants were above the cut off for depression.

3.4.5. Fatigue

The average level of fatigue reported fell above the cut-off level. Approximately 60% of participants' scores were above the 36 cut-off for fatigue levels.

3.4.6. Dexterity

Upper limb function was considered to be in the mild range according to the 9HPT. Scores on the GPT were considerably higher, which reflects the additional sensori-motor demands of the task.

3.4.7. Visual functioning

The mean HCVA for the sample fell within the range for 'normal vision'. While the average LCVA for both 2.5% and 1.25% was considered 'moderate visual impairment'. The LCS was below that signifying normal contrast sensitivity, but above the score for visual impairment.

Table 5. *Premorbid functioning, mood, fatigue, dexterity and visual functioning*

Associated factors	m (sd)	Range
TOPF	110 (12)	86-136
HADS-A	8 (4)	2 -17
HADS-D	6 (3)	0 – 14
FSS	42.75 (13)	9 – 63
9HPT	24 (7)	17 – 50
GPT†	111 (44)	62 – 242
MPI†	86 (34)	43 – 208
HCVA	.10 (.17)	-.18 - .50
LCVA 2.5%	.50 (.16)	.03 - .86
LCVA 1.25%	.73 (.10)	.50 - .94
LCS	1.89 (.21)	1.15 – 2.15

Note. Fatigue Severity Scale (FSS); Grooved Peg Test (GPT); High Contrast Visual Acuity (HCVA); Hospital Anxiety and Depression Scale – Anxiety (HADS-A); Hospital Anxiety and Depression Scale – Depression (HADS-D); Letter Contrast Sensitivity (LCS); Low Contrast Visual Acuity (LCVA at 2.5% or 1.25%); mean (m); Motor Planning Index (MPI); Nine Hole Peg Test (9HPT); standard deviation (sd); Test of Premorbid Functioning (TOPF). †n=38.

3.4.8. Cognitive tests

The results from the BICAMS tests are reported in Table 6. Three one-way random effects ICCs conducted between the versions of the BICAMS demonstrate above satisfactory levels of agreement. The ICC was greatest for the SDMT, followed by the BVMT-R and CVLT-II.

Standard administration of BICAMS is reported to take under 15 minutes to complete. The average duration of administration of the BICAMS iPad in the current study was recorded as 13.21 minutes (sd= 2.61), which ranged from 8 to 25 minutes.

The order of administration of the BICAMS was evaluated across six one-way ANOVAs, since half of participants completed iPad BICAMS first and the other half completed paper and pencil BICAMS first. Using Bonferroni correction for multiple testing, one ANOVA was statistically significant ($F(1, 39)=19.754$, $p<.001$). The results show that performance on CVLT-II was poorer if participants were in a condition which received the paper version first. The results could be attributed to the superior internal validity of the iPad BICAMS (e.g. display times, reading times) compared to the paper and pencil version which may be limited by examiner error. The iPad BICAMS provides a cue for when the examiner should give the verbal stimuli in the CVLT-II, while the examiner uses a stopwatch as a guide when administering the paper and pencil version. The findings may not have been found in the opposite direction, due to practice effects.

An index of cognitive impairment calculated based on iPad BICAMS scores showed the following distribution. Two people scored less than 2 standard deviations from the published norms on the SDMT. While 10 participants scored less than 1 standard deviation from the published norms for that subscale. For the BVMT-R, 2 people scored less than 2 standard deviations from the published norms. There were 6 participants who scored less than 1 standard deviation from the published norms on the BVMT-R. In the CVLT-II, only five participants scored less than 1 standard deviation from the published norms. All of the remainder of scores were greater than or equal to the published norm. There was no significant difference between impairment on either subscale ($F(1, 78)=2.646$, $p=.077$).

Table 6. *BICAMS performance and level of agreement*

		m	(sd)	Interclass correlation
SDMT	iPad	50.13	(14.37)	.85, 95% CI (0.74, 0.92), p <
	Paper	47.83	(12.33)	.001
CVLT-II	iPad	55.73	(17.10)	.57, 95% CI (0.32, 0.75), p <
	Paper	53.68	(14.01)	.001
BVMT-R	iPad	23.40	(10.69)	.67, 95% CI (0.45, 0.62), p <
	Paper	23.30	(8.12)	.001

Note. Brief Visual Memory Test Revised (BVMT-R); California Verbal Learning Trials II (CVLT-II); mean (m); standard deviation (sd); Symbol Digit Modalities Test (SDMT).

3.4.9. Correlations Analysis

A series of bivariate correlations were performed to understand the individual associations between iPad BICAMS subscales and associated variables (see Table 7). Only the following associations were significant following Bonferroni correction for multiple testing. The SDMT was significantly negatively related to MPI (r = -.469, p =.002). The BVMT-R was significantly negatively related to HCVA (r = -.459, p =.003). No other correlation analysis reached statistical significance. Motor and visual function are not necessary for immediate verbal auditory recall (CVLT-II), therefore correlations were not performed for between these variables. Fisher's z-transformation was performed to obtain confidence intervals for the correlations. The confidence intervals for the above correlations overlap with 0 and so the effects will no longer be significant (SDMT and MPI: CI= .08, .73; BVMT-R and HCVA: CI= -.72, -.07).

Table 7. *Correlations between iPad BICAMS performance and associated variables*

	iPad SDMT	iPad CVLT-II	iPad BVMT-R
HADS-A	*r*= .175, p= .280	*r*= .044, p= .788	*r*= .046, p= .776
HADS-D	*r*= .007, p= .965	*r*= -.060, p= .714	*r*= .039, p= .811
FSS	*r*= -.077, p= .639	*r*= .056, p= .734	*r*= .002, p= .988
MPI	*r*= -.469, p= .002	-	*r*= .028, p= .863
HCVA	*r*= -.205, p= .204	-	*r*= -.459, p= .003
LCVA 2.5%	*r*= .397, p= .011	-	*r*= -.283, p= .077
LCVA 1.25%	*r*= -.192, p= .276	-	*r*= -.275, p= .115
LCS	*r*= .196, p= .226	-	*r*= .318, p= .045

Note. Fatigue Severity Scale (FSS); Motor Planning Index (MPI); High Contrast Visual Acuity (HCVA); Hospital Anxiety and Depression Scale – Anxiety (HADS-A); Hospital Anxiety and Depression Scale – Depression (HADS-D); Letter Contrast Sensitivity (LCS); Low Contrast Visual Acuity (LCVA at 2.5% or 1.25%); Brief Visual Memory Test Revised (BVMT-R); California Verbal Learning Trials II (CVLT-II); Symbol Digit Modalities Test (SDMT).

A linear regression revealed a significant relationship between MPI and SDMT ($p < 0.001$). The slope coefficient for gestation was - 0.08. The R2 value was 0.22 so 22% of the variation in SDMT can be explained by the model containing only MPI.

3.4.10. Participant feedback

Seventy percent of participants reported that they would be 'moderately' to 'very satisfied' to be tested by the BICAMS iPad on a yearly basis in the future. Participants scored the level of enjoyment and ease exactly the same between iPad and paper

versions of BICAMS. There was no discernible difference between preferences of either version of BICAMS. More participants rated that they had no preference over iPad version (n=16, 40%), than those that stated favouring either the iPad (n=12, 20%) or paper BICAMS (n=12, 20%). The written feedback from participants who stated a preference was reduced into the following categories: ease of testing, an element of independence on test, favouring interacting with technology, engagement with tests, enjoyment of the test and maintaining a level of control while being tested. Response rates were too low to perform formal analysis of the categories.

3.5. Discussion

Cognitive impairment is amongst an array of symptoms in MS (Benedict & Zivadinov, 2011). Assessing cognition is of vital importance since cognitive impairment is related to a host of poor outcomes. Comprehensive neuropsychological batteries offer advantages over patient report, clinical interview and MRI which lack specificity (Rocca et al., 2015; Romero et al., 2015). However these batteries often take a long to conduct and require access to specialist materials and training.

The BICAMS was developed in 2010 to optimise cognitive assessment in MS. The test can be completed in under 15 minutes by most healthcare professionals. While MRI parameters do not correlate well with cognition (Mollison et al., 2017), the BICAMS offers an objective way to assess the three most impaired domains of cognition, which include the SDMT for IPS, the CVLT-II for immediate verbal recall and the

BVMT-R for immediate visual memory. For best part of the last decade the BICAMS has become increasingly adopted as an objective tool to assess cognition in MS. In 2018 the BICAMS iPad was developed, with the objective to further refine the validity of the assessment. With all physical parameters kept constant with the paper version, the iPad BICAMS offered the addition of automated scoring and presentation times and assessment of visual functioning and drawing ability.

Thus the primary aim of this study was to investigate the level of agreement between the iPad BICAMS and the paper version. The secondary objective was to explore relationships between associated factors, such as premorbid functioning, mood, dexterity and visual functioning, and cognitive performance on iPad BICAMS. The final aim was to explore participant's experience of using iPad BICAMS.

In line with the first hypothesis the level of agreement between the BICAMS iPad and the paper version was above that considered to be satisfactory on all scales. The agreement was particularly strong between the SDMT scales, compared to the CVLT-II and BVMT-R. The SDMT has previously been recommended by an expert committee to be the most reliable, valid and sensitive screening test for cognitive impairment in MS (Langdon et al., 2012). The SDMT is more accurate in defining cognitive impairment than self-report (Kim et al., 2017). The IPS was been presented as the primary cognitive deficit in MS (Costa et al., 2016). The findings of this study provide support for this to some extent, although the SDMT task does require aspects of visual memory and oral-motor ability (Patel, Walker, & Feinstein, 2017b).

The finding of a moderate level of agreement between the CVLT-II and BVMT-R iPad and paper forms is not unsuprising. This could be explained by a number of factors. Firstly, previous literature has suggested that cognitive impairment in the domains assessed by these tasks are second to that of IPS dysfunction (e.g. Grzegorski & Losy, 2017). Secondly, while the psychometric properties of these tests in MS are good they include the delayed recall condition. Therefore they should be interpreted cautiously when evaluating cognitive performance.

Cognitive impairment, which ranged between 1.5 – 2 standard deviations below the healthy norm, was 30% in the current study. This is relatively low compared to the reported prevalence in other studies. A recent large multicentre trial reported approximately 50% of those with RRMS had a cognitive impairment (Ozakbas et al., 2017). Cognitive impairment in the current sample may have been lower than that reported in previous literature for a number of reasons. Firstly, most participants had RRMS compared to SPMS or PPMS, cognitive impairment is more common is progressive forms of the disease. Secondly, the premorbid intelligence of the sample was above average. Greater premorbid functioning is a protective factor against cognitive decline (Chillemi et al., 2015). Thirdly, half of participants were taking the same medication, DMDs slow disease progression, which potentially includes against cognitive decline.

The iPad BICAMS shows a similar level of internal validity as other cognitive assessments developed for neurodegenerative populations. The CADi showed alpha values over 0.7 (Onoda et al., 2013) and the C3-PAD had excellent validity between home and treatment conditions (0.93) (Rentz et al., 2016). Similar to the paper

version, the testing time took under 15 minutes. An order effect was observed in the CVLT-II subscale, with a trend for better performance if the paper version was administered first. This could be interpreted in the context of increased validity of the iPad version of the test supported with automated pacing of stimuli.

To investigate the second hypothesis, the exploratory analysis revealed only an inverse association between MPI and iPad SDMT. High contrast visual functioning was related to the BVMT performance. The MPI was found to predict scores on the SDMT. This finding is not unexpected as most individuals with MS have an upper limb dysfunction (Lamers & Feys, 2014). It is interesting to note by the direction of this association, which suggests that upper limb function and cognitive ability are not synchronous. In addition, HCVA has been found to remain functional in people with MS (Balcer et al., 2017). Since the geometric figures in the BVMT-R are presented at a high contrast level, it can be expected that HCVA would correlate with performance in this domain.

It was surprising to find that mood and anxiety did not correlate with performance on the iPad BICAMS. Since depression and anxiety are the most commonly experienced mental health problems in MS (Turner et al., 2016). It has been reported that mood may impact on cognitive performance in MS (Nunnari et al., 2015), in domains including IPS and visual memory (Morrow et al., 2015). Depression has been shown to account for around a 20% reduction in processing speed on the SDMT (V. Patel & Feinstein, 2018). The lack of a relationship between depression and cognitive performance might be explained by depression scores being in normal range in the current study. In addition other studies have used alternative self-report

methods, including the BDI (e.g. Golan et al., 2018), which may be influenced by somatic symptoms.

In addition, we found that fatigue did not correlate with cognitive performance. As most of the sample reported high levels of fatigue it was expected this would influenced cognitive ability, in areas such as visual processing (Kluckow et al., 2016), memory and attention (Pokryszko-Dragan et al., 2016). In addition, premorbid intelligence was not found to be related to neuropsychological functioning (Benedict & Zivadinov, 2011). These deviations from expectations may have been related to issues of statistical power.

The third hypothesis was marginally supported since the majority of participants rated that they would be 'moderately satisfied' to 'very satisfied' to be tested by the BICAMS iPad on a yearly basis in the future. Participants were indifferent about the BICAMS format, there was no difference between preferences of either version of the BICAMS. For those that did state preferences, there was a trend for participants to prefer to use the paper version for ease.

3.5.1. S*trengths*

There are many positive features of this study which need to emphasised. Firstly, the use of a standardised and validated battery within the MS population limits bias. The materials selected have already been shown to be sensitive within this group. Randomising the order of testing of the iPad or paper BICAMS, supported with exploring the impact of order effects. The CVLT-II was found to be most influenced

by this. Therefore it is likely that the automated timing of the word list in the iPad BICAMS improves internal validity to some extent within that subscale.

Secondly, this was the first study to include a measure of participant experience of the BICAMS assessment. Participant experience is an important factor to have considered. Understanding how people with MS perceive cognitive assessment could improve engagement with neuropsychological tasks. Particularly if the iPad BICAMS is used as intended on a yearly basis.

Thirdly, only a single data point from iPad was not uploaded correctly from a sample of 40 participants. This means that the iPad BICAMS has a relatively low error rate. Thus healthcare professionals using the tool can be quite confident in its reliability. Particularly in busy clinic settings where the iPad BICAMS may be used up to several times a day.

3.5.2. Limitations

There are some shortcomings of this research which need to be considered. Firstly, response rate was not recorded for the study; therefore it is unclear about how representative the current sample is. Also the study was underpowered as it did not reach the suggested sample size. This may have impacted on statistical analysis between the iPad BICAMS performance and associated factors, including premorbid intellectual functioning, dexterity, mood and visual functioning. This was shown by the mild effect size of the correlation and that the confidence intervals overlapped

with zero (Greenland, Senn, Rothman, Carlin, Poole, Goodman & Altman, 2016). Therefore it is likely that the study was underpowered by the sample size.

Secondly, the sensitivity of the visual function test may have been compromised by testing in different lighting environments, including participant home and hospital. However attempts were made to maintain consistency between testing environments to reduce bias.

Thirdly, the majority of those who participated had RRMS phenotype. Fewer still had SPMS or PPMS, which prevented exploration of cognitive ability between groups. This is an important point since cognitive impairment is thought to be most marked in progressive forms of the illness. A recent meta-analysis showed that cognitive impairment, in the domains of memory was worse in individuals with PPMS compared to RRMS (Johnen et al., 2017), which will have clinical implications for targeted treatment.

3.5.4. Future directions

The iPad BICAMS has been successfully shown to have a moderate to high level of agreement with the paper and pencil form. There could be several ways which the iPad BICAMS could be validated in the future. Firstly, through reporting the internal consistency of the scale using Cronbach's alpha. This may be particularly important for the CVLT-II and the BVMT-R immediate trials where psychometric properties were established for the assessments which include the delayed recall condition.

Secondly, to compare statistically between the internal validity of the BICAMS paper and pencil form and the iPad version.

It will be important to establish the level of reliability of the iPad BICAMS through test re-test and follow-up designs. This would support the application of the BICAMS iPad within routine clinical appointments. This would improve understanding of the profile and trajectory of cognitive functioning in RRMS particularly. It will be crucial to develop thresholds of clinical significance for BICAMS iPad scores, since it has been proposed that SDMT change approximating 4 points or 10% in magnitude is clinically meaningful (Benedict et al., 2017).

It will be important to investigate the predicative validity of iPad BICAMS in identifying those at high risk of disability progression and poor clinical outcome (Pitteri, Romualdi, Magliozzi, Monaco, & Calabrese, 2017). The next steps will be using cognitive test performance alongside structural and functional imaging methods to improve validity of cognitive assessment associations (Benedict et al., 2017)

It will be necessary to use BICAMS iPad in trials of novel pharmacological treatments aimed at reducing cognitive impairment in MS (e.g. Cinar et al., 2017). A recent review discussed the pharmacological interventions for MS and highlighted novel strategies, such as cryostimulation, to target cognitive impairment (Miller, Morel, Redlicka, Miller, & Saluk, 2017).

3.5.5. Conclusion

In summary, it has been demonstrated that the iPad BICAMS reaches the same level of agreement was the BICAMS paper version to assess cognition in MS. IPS appears to be related to motor planning.

4. Integration, Impact and Dissemination Summary

4.1. Introduction

Multiple Sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS) (Thompson et al., 2018). Cognitive deficits are among several other forms of physical impairments. Half of individuals with MS will have a cognitive impairment (Benedict & Zivadinov, 2011).

4.2. Integration

In this section I reflect on the process of integrating the chapters presented in the thesis. I discuss the extent to which I was able to unify the subcomponents, in what way I achieved this, and the context in which the final form took. As part of this section I highlight the importance of self-reflexivity in conducting research and what implications this had for the project in its final form.

There are many different factors which determine the extent to which the subcomponents of the thesis were fully integrated. From a personal perspective I feel as though cohesion between the chapters was achieved to a significant degree. There is a clear argument which runs centrally through the pieces of work and most of the literature referenced in each section is repeated between the chapters which, to me, suggests that the thesis is well embedded within the wider evidence-base, as well as demonstrating a logical advancement to the field. In addition the chapters

can be considered to standalone as they offer novel and distinct contributions. In this way the thesis has achieved its original purpose.

I felt that the chapters presented in the thesis were integrated well for a number of reasons. Firstly, the primary focus of the work was specific on a specific instrument. Having this anchor between the chapters supported with my clarity of thought and written expression. Throughout this project I found that decision making was simpler for this reason, which kept the project neat and contained.

As an example, in the initial stages of supervision we discussed conducting a number of possible systematic review topics. We were clear from the beginning about the content of the empirical study. I decided to take forward the current idea, which was a review of the BICAMS validation studies, as other options felt too broad (i.e. quality of life in MS) and less central to the focus of the content of the empirical chapter. I was conscious about creating an overall narrative which built pragmatically from the systematic review through to the empirical study.

In addition, once recruitment had ended on the iPad validation study I was able to visually compare performance on iPad BICAMS to those scores published in the BICAMS validation studies. It was comforting to observe that performance on the iPad BICAMS subscales were within the ranges of those studies published as part of the international validation protocol. For me, this was further confirmation that cohesion between the two chapters had been achieved.

Secondly, I found that supervision was essential in managing synergy between the subcomponents. A clear research aim was set from the beginning which was

maintained by regular communication, a shared agenda and plan of actions. I found that in-between supervision rapid plan–do–study–act (PDSA) cycles took place (Taylor et al., 2014), which often presented novel challenges. I felt that supervision provided consistency throughout the project which prevented drift from the research aims at times when new or unexpected information could have redirected the course.

I found that this was particularly the case during the initial planning stages of the thesis. I had no experience of MS prior to undertaking the research project and only a limited understanding of the evidence-base in the field. I reflected that as a Trainee Clinical Psychologist, I felt privileged to have been supervised by two Professors who each have a strong international research portfolio. With this support I was able to quickly improve my understanding of MS. This, in addition to, interactions with participants, enabled me to transfer my knowledge from theory to practice. From these experiences I was able to critically reflect on the BICAMS and thus confidently develop Discussion sections about the tool.

Thirdly, the process of writing was cyclical and I found myself occupying many meta-views in the development of the final form. I was aware of keeping in mind the agreements from supervision, the course requirements, how to maintain the confidentiality of service-users and to acknowledge the support of the neurology team at the Royal London Hospital. This type of writing process is quite typical. According to the cognitive process theory of writing (Flower & Hayes, 1981), the interaction between the writer's defined topic, audience and writing plans and the

components of the writing process, including planning, translating, reviewing and monitoring, can occur individually or in tandem, in any order or repeatedly.

Having conducted the systematic review first followed by the empirical chapter, I could see the value and potential of the iPad BICAMS. I found that being able to understand the importance and need to conduct the empirical study supported me to focus my thoughts and motivate me to complete the project. I remember feeling surprised by the number of countries that had participated in the international validation protocol. From reading their articles, as part of conducting the systematic review, I felt confident to describe the link between the systematic review and empirical chapter.

The final form was developed through an accumulation of processes of positive interactions between various stakeholders, including myself, my supervisors, the course research subcommittee, the NHS ethical approval processes, the recruitment site and the participants. This dynamic was not always straightforward and I found that a challenge was managing multiple demands simultaneously. The subcomponents were developed in different timescales, which was useful as the outcomes could be translated through to the other working subcomponents. For example, in reviewing the validation studies I was aware of the descriptions of the task, and so I focused on explaining this in systemic terms (e.g. who delivered the task, their profession, their training).

A potential challenge to the completion of the final form was my involvement in all aspects of the project, in particular, I was not blind to the hypothesis and aware of

the direction anticipated and I administered the tasks. I wonder what this bias may have contributed to in terms of the overall project. A benefit of this study was the inclusion of the participants' experience survey, where participants were given the opportunity to express their views openly about the BICAMS. I found that this was refreshing and allowed service-users to have an active voice within the final form. For me, this contribution added an estimation of ecological validity which had been omitted from the initial plans for the thesis. The decision to develop and include the survey came later after the initial planning stages, but has proved integral to our understanding about the validity of BICAMS.

A further aspect to consider, in terms of integration is the link between the findings in the study and its practical applications. I felt that I could make quite direct links between how the BICAMS iPad version could be realistically used across services and knowing this was both rewarding and motivating which helped me to drive forward to complete the piece of work.

4.3. Impact

The novel and distinct contributions within this thesis, which include the production of the systematic review and the empirical study, have a significant impact on clinical psychology for a number of reasons which have been outlined below.

Firstly, related to the selection of the most effective form of cognitive assessment. Although the paper and pencil BICAMS has increased the availability of cognitive assessment within MS, by requiring less training to administer and improved

accessibility outside of MS specific centres, there was need for the development of the iPad version. The iPad BICAMS has demonstrated good psychometric properties within the empirical study, which suggest that it will have a great impact on future cognitive assessment in MS. This is primarily for six reasons, since it: (a) has increased the validity of the tool, which includes timings and automatic scoring (the latter will be available for the BVMT-R shortly); (b) has allowed for clinical assessment and management of cognitive performance to be more widely available; (c) has improved participant engagement with cognitive assessments, participants' reported that the would be highly agreeable to be tested via the iPad BICAMS on a yearly basis in the future; (d) has demonstrated psychometric rigour which will enable drug trials involving pharmaceutical companies, such as Novartis, to use computerised assessments of cognition; (e) with enabling of the former benefit, to develop more drugs with MS therapeutic efficacy; and (f) will be linked with Electronic Health Records (EHR), which are increasingly being adopted and invited in within the United States (69%) and Canada (57%) (Borycki, Newsham, & Bates, 2013).

Secondly, related to the profile of cognitive assessment in MS. It is highly likely that the meta-analysis of the BICAMS scores generated from the international validation protocol can be used as supporting evidence for the importance of conducting cognitive assessments in routine clinical appointments. This could be through supporting with cases to spend part of clinical budgets on two iPads to run the BICAMS software. Up until the production of the BICAMS validation studies there had not been a tool which had been consistently applied to assess cognition in MS

internationally. The pooled sample size of the individuals with MS included in the meta-analysis was 1,599. Therefore the demonstrated validity of the BICAMS across countries could encourage its use in countries which have yet to validate the BICAMS. Understanding and confidence in the BICAMS may have been improved in the MS community at large.

Thirdly, the development of the thesis marks the success of the international collaboration to improve cognitive assessment in MS. The cooperation of the international MS community has been ongoing since recommendations for the BICAMS were published in 2010 (Langdon et al., 2012). The BICAMS appears to have now superseded its predecessors and has been widely adopted as the most common form of cognition assessment in MS. It is likely that the findings in the thesis will therefore have a significant impact in research terms. As described in the chapters within the thesis, there are many points of interest to study, such as the association between BICAMS performance and quality of life, efficacy of disease modifying drugs (DMDs) and test re-test reliability of the tool.

Perhaps among the most important questions will be related to treatment. Specific cognitive rehabilitation for MS is arguably the most effective form of intervention. It is possible that the findings of this thesis could be used as evidence to support the use of the BICAMS in clinical trials of cognitive rehabilitation. Several previous systematic reviews described that the heterogeneity of the evidence surrounding cognitive rehabilitation in MS was less than satisfactory. Therefore there is a strong case for the use of the BICAMS as a standard measure of cognitive ability across study trials to examine the effectiveness of cognitive rehabilitation.

Fourthly, related to translating the findings of the thesis across to theoretical orientations about cognition in MS, the meta-analysis showed that IPS was reduced in people with MS compared to HC, with a largest effect size. This is consistent with earlier literature which reported that IPS is the most prevalent cognitive impairment in MS. It had been previously proposed that IPS presents as the core cognitive deficit (Costa et al., 2016). Although the results from this thesis are unable to confirm or disconfirm this notion at present, they will, however, contribute incrementally towards to the long term better understanding of models of cognition in MS.

Given the cross-sectional nature of the study designs and lack of randomization between participants in the articles included in the systematic review it is unclear whether reduced IPS is a contributor to or consequence of impairments in other domains. However, given the overall finding it is highly likely that impaired IPS plays an important role in cognitive dysfunction in MS.

Interestingly a medium effect size was found between both immediate recall tests, which could suggests that MS impacts on verbal and visual recall in a similar way. Earlier theories pointed to difficulty with immediate verbal recall being a result of a deficit in acquisition than retrieval. It could be suggested that acquisition of visual information is impaired in MS. This may be facilitated by visual acuity impairments, particularly related to LCVA than HCVA, as this was found to be non-affected in people with MS in the current empirical study. Further research will need to be conducted regarding the model of cognitive impairment in MS to support this interpretation.

Fifthly, I have reflected on the process of developing this thesis and the impact that it has had on me, in terms of my own personal and professional development. As I stated earlier, I had no prior experience of working with individuals with MS. Fortunately I had been able to complete several neuropsychological placements as part of training, which helped me to feel confident about conducting research regarding neuropsychological assessment.

While collecting data I noticed that as the literature had explained, MS symptoms were broad and varied. I had expected that most participants would be in wheelchairs. However I was surprised and comforted to learn that DMDs were able to reduce the mobility deterioration. I was particularly taken aback by participants' performance on the Grooved Peg Test (GPT). I had not administered this assessment before so I had limited expectations about participants' performance. Many participants completing this test challenging. It was difficult for me to observe participants in a moment of frustration. I reflected that this assessment, and others included in the battery, produced this response as they were sensitive to detect specific impairments in MS.

When analysing the results it came as no surprise to me that the average sample premorbid intellectual function was above average. From listening to participants' stories it was clear how MS had negatively impacted on their ability to carry out tasks which they had previously been able to perform well on. I noticed myself empathising with their position, understanding their loss motivated me to want to support them and others with MS with the validation of the iPad BICAMS.

4.4. Dissemination

Dissemination of the intervention to the specific audience forms an integral component of the Division 12 Task Force of the American Psychological Association, which aims to promote and support the integration of clinical psychological theory within practice. For the purposes of this research the intended audience is the MS community of individuals with MS and their families, clinicians and researchers, services and support groups.

I based the dissemination plan for this audience on the guidance that the most effective form of dissemination in clinical psychology involves the adaption of the medium and language of the communication to suit the specific audience (Smith & Thew, 2017). Therefore the findings from the current thesis, which have been described in the systematic review and empirical study chapters, will be disseminated widely, across a range of settings, to a large audience and in a variety of formats.

4.4.1 Electronic dissemination

Publication in peer-reviewed journals has been described as one effective method of sharing findings (Smith & Thew, 2017). At the time of writing this, I have submitted the systematic review and meta-analysis chapter for publication in the electronic peer reviewed scientific journal Neurology and Therapy. It was an invited review

which was accepted for publication in May 2018. The journal is relatively new and originated in the United States in 2012. It has a wide focus on observational, real-world, and health outcomes research around the discovery, development, and use of neurological and psychiatric therapies, including devices.

The paper published in this journal is likely to attract a large audience, given that it is open access and is published in the English language. Earlier research has outlined that English proficiency was one of the factors strongly associated with publication in the highest ranked general medical journals (Man, Weinkauf, Tsang, & Sin, 2004). Unfortunately, whilst it might be optimal to translate this publication, I do not have capacity to do this at present. This is a limitation in the dissemination plan, since MS has been shown to impact those individuals in non-English speaking countries (Browne et al., 2014). Despite this shortcoming, the paper was accompanied by a bulleted summary slide, which offered a time-efficient way of sharing the information from the article.

The empirical study chapter will be written up for publication in a peer reviewed scientific journal following submission of this thesis. The target journal for this will be Multiple Sclerosis, which is a peer-reviewed journal which originated in the United States in 1995. This journal was selected as its scope is on the aetiology and pathogenesis of demyelinating and inflammatory diseases of the central nervous system and on the application of such studies to scientifically based therapy. In addition this journal has a high H Index at 101.

In addition to dissemination in journal format, I plan to publish a summary of the study in other forums, including via the MS Trust and MS Society. There are two main benefits of this type of dissemination for improving access, firstly that this time they will be written up as articles by patients with MS and secondly they will be published as newsletters or on the appropriate website for the specific audience. The MS Trust and MS Society are well established organisations that have a high profile within the MS community. Including service-users in dissemination is a critical feature of the dissemination process, since service-users can consult on the promotion of the research (Tabak, Khoong, Chambers, & Brownson, 2012), since the background of the person sharing the information can influence the speed at which the innovation is disseminated (Cockerill & Barnsley, 1997).

I cited Royal Holloway, University of London, as both my and my Supervisor's affiliation on the publication. The publication of this paper is likely to have a positive impact on the research capital of Royal Holloway, University of London, since the quality of research outputs, including publications, in the United Kingdom are assessed by the Research Excellence Framework (REF). Further, the publications will contribute my supervisor's impact case for the department. In 2014 Royal Holloway was ranked within the top 25% of universities in the UK for research which is recognised as being 'world leading' (Holloway, 2014). This recognition may promote the research further among those involved in research within the MS community.

The thesis, including the systematic review and empirical study chapter, will be submitted to the Doctorate in Clinical Psychology at Royal Holloway University of London and the electronic version be made publically freely available in PDF format

to download and view. This may further promote the research among student populations with MS.

4.4.2. Non-electronic forms of dissemination

Further to written channels of dissemination, the results will be shared in oral form. I will orally present the study summaries of the empirical study chapter at Royal Holloway, University of London's Doctorate in Clinical Psychology research presentation day. In the audience will be Trainee Clinical Psychologists and Chartered Clinical Psychologists. This form of dissemination will involve peer-to-peer information sharing and will promote understanding of cognition in MS to those who will practice as clinical psychologists and may even work in services with those with MS. A benefit of this in-vivo form of dissemination is that audience members will be given the opportunity to pose questions directly to me and my supervisor following the presentation which may enhance awareness.

I will conduct a second oral presentation for the Neurology service at the Royal London Hospital, which was the site for recruitment. The team includes neurologists, a clinical trails manager and clinical nurse specialists. This service hosts a number of research trials and my supervisor manages an MS website which is accessed by a large number of the service-users. I plan to write a study summary for the supervisor to publish this on his website (GG). I hope that this form of dissemination to those that work within MS will improve the awareness and recognition of cognitive impairment within MS. This form of promotion is important as the attitudes of mental health service providers can facilitate the effectiveness of dissemination

efforts (Aarons, 2004). It has been reported that having respected opinion leaders promote the research can be a more effective form of dissemination (Oxman, Thomson, Davis, & Haynes, 1995).

I plan to provide a third oral presentation about the empirical study, which will be at a large international scientific conference. I have written up the results of the systematic review into the form of an abstract which has been submitted for a presentation at the European Committee for Treatment and Research in MS (ECTRIMS) annual meeting. ECTRIMS has been running for over 25 years and was chosen for dissemination as it has served as the world's biggest scientific meeting about MS every year. Access to the conference comes at a fee, therefore there may be issues around my being able to present it. However at this conference delegates are encouraged to discuss their reflections through social media, including Twitter. Anybody following publically available accounts will be able to access short reflections about the study in this way.

In sum, the particulars of this research have been, or are planned to be disseminated in a variety of written and oral forms, the former by both researcher and service-user, through a wide range of channels, including online, newsletters, presentations, posters, and to a different audience, including online, in vivo and social media, with the intention of promoting the field of cognition in MS.

4.5. Conclusion

The purpose of this thesis twofold, firstly to synthesise the BICAMS studies which had been produced as part of the international validation protocol and secondly, to validate the newly developed iPad BICAMS in a UK sample. The systematic review and empirical study focused on each of these individual aims. I reflected on how well I thought these two elements were integrated drawing from examples from the research process. I generally felt that both pieces work were embedded well within the existing literature base, particularly because of the focus on one instrument. The findings generated from each chapter are likely to have a significant impact in the field of cognitive assessment in MS. I discussed the likely areas of impact, including improving the profile of cognitive assessment in MS, contributing towards theoretical models of cognition in MS, influencing countries to participate in the international validation protocol and my own personal and professional development. Various methods of dissemination were highlighted to inform the MS community of the findings contained within the thesis. In conclusion, this thesis has shown that the BICAMS is an internationally valid tool to assess cognition in MS and that its predecessor, the iPad BICAMS, is a psychometrically sound and participant endorsed tool to assess cognition.

5. References

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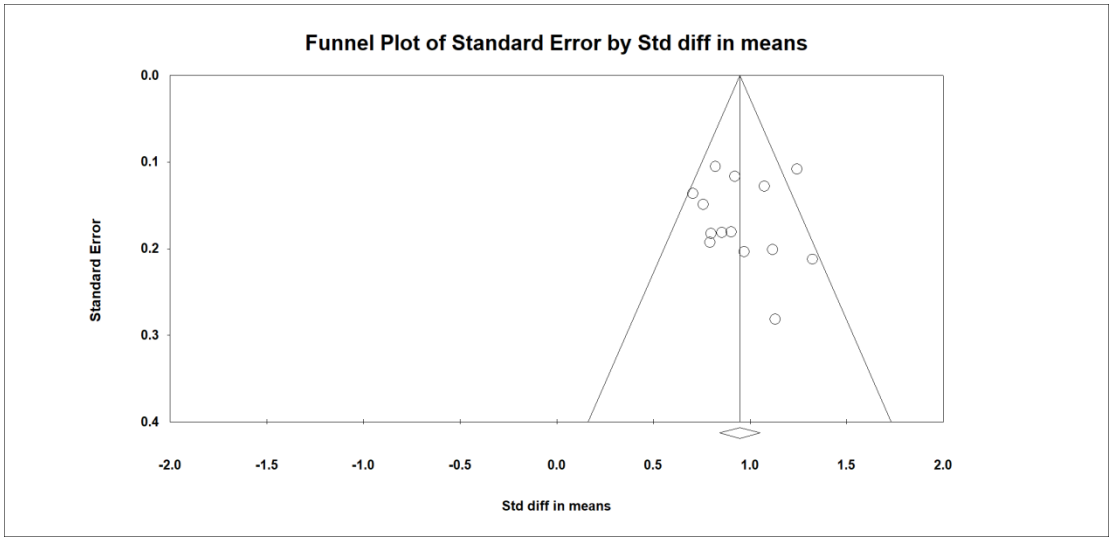
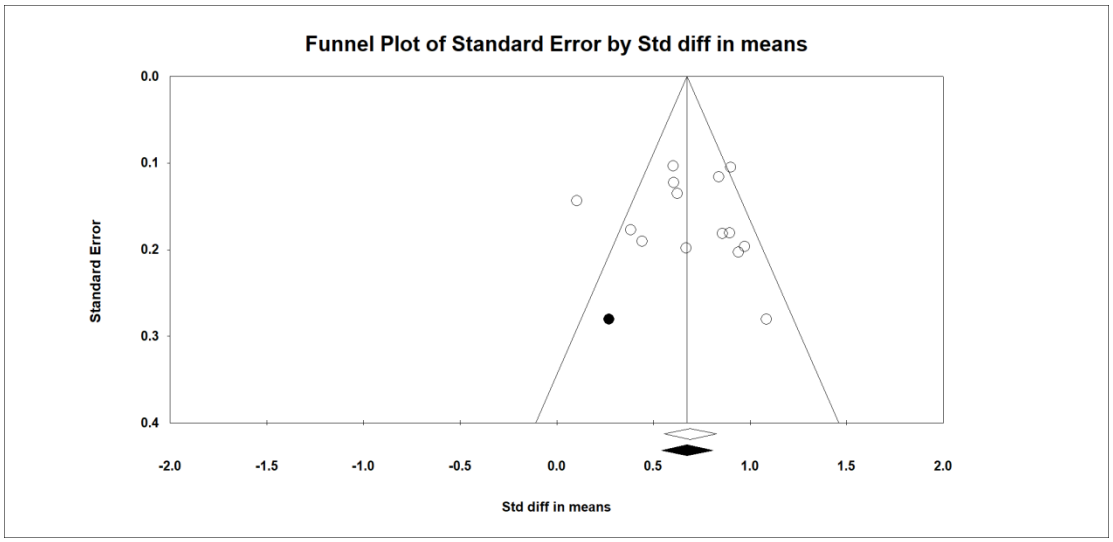
6. Appendix

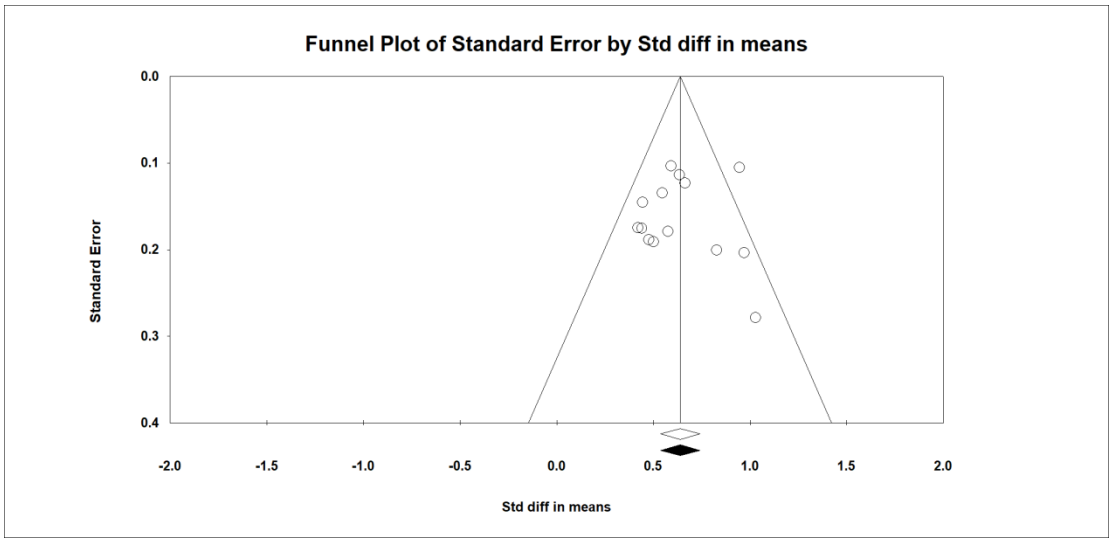
6.1. Funnel Plot of the Symbol Digit Modalities Test (SDMT)



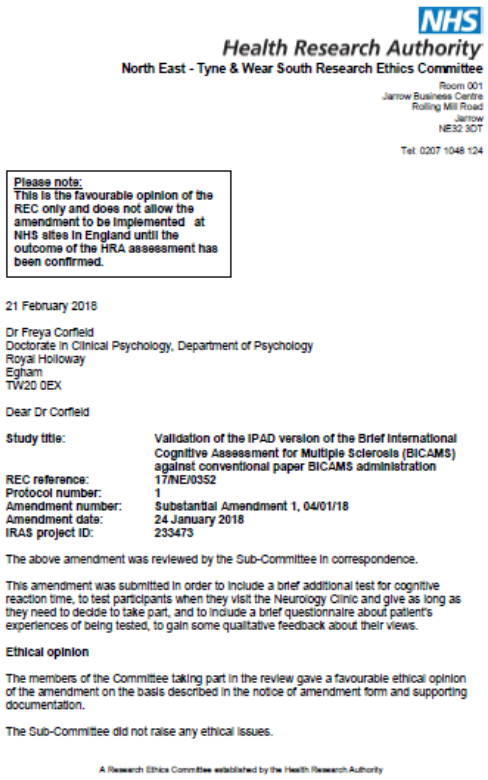
6.2. Funnel Plot of the California Verbal Memory Test II learning trials (CVLT-II)



6.3. Funnel Plot of the Brief Visual Memory Test learning trials (BVMT-R)



6.4. Ethical Approval for Empirical Study



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North East - Tyne & Wear South Research Ethics Committee

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Please note:
This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

21 February 2018

Dr Freya Corfield
Doctorate in Clinical Psychology, Department of Psychology
Royal Holloway
Egham
TW20 0EX

Dear Dr Corfield

Study title:	**Validation of the IPAD version of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) against conventional paper BICAMS administration**
REC reference:	**17/NE/0352**
Protocol number:	**1**
Amendment number:	**Substantial Amendment 1, 04/01/18**
Amendment date:	**24 January 2018**
IRAS project ID:	**233473**

The above amendment was reviewed by the Sub-Committee in correspondence.

This amendment was submitted in order to include a brief additional test for cognitive reaction time, to test participants when they visit the Neurology Clinic and give as long as they need to decide to take part, and to include a brief questionnaire about patient's experiences of being tested, to gain some qualitative feedback about their views.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The Sub-Committee did not raise any ethical issues.

A Research Ethics Committee established by the Health Research Authority

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP)	Substantial Amendment 1, 04/01/18	24 January 2018
Other [Procedure Flowchart]	2	04 January 2018
Other [Experience of BICAMS questionnaire]	1	04 January 2018
Participant consent form	3	04 January 2018
Participant information sheet (PIS)	3	04 January 2018
Research protocol or project proposal	3	04 January 2018

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

17/NE/0352: Please quote this number on all correspondence

Yours sincerely

pp.

Mr Paddy Stevenson
Chair

E-mail: nrescommittee.northeast-tyneandwearsouth@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Professor Andrew MacLeod, Royal Holloway*

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01 February 2018

Dr Freya Corfield
Doctorate in Clinical Psychology
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Royal Holloway
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TW20 0EX

Dear Dr Corfield

Study title: **Validation of the IPAD version of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) against conventional paper BICAMS administration**
REC reference: **17/NE/0352**
Protocol number: **1**
Amendment number: **Substantial Amendment 1, 04/01/18**
Amendment date: **24 January 2018**
IRAS project ID: **233473**

Thank you for submitting the above amendment, which was received on 25 January 2018. I can confirm that this is a valid notice of a substantial amendment and will be reviewed by the Sub-Committee of the REC at its next meeting.

Documents received

The documents to be reviewed are as follows:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP)	Substantial Amendment 1, 04/01/18	24 January 2018
Other [Procedure Flowchart]	2	04 January 2018
Other [Experience of BICAMS questionnaire]	1	04 January 2018
Participant consent form	3	04 January 2018
Participant information sheet (PIS)	3	04 January 2018
Research protocol or project proposal	3	04 January 2018

Notification of the Committee's decision

The Committee will issue an ethical opinion on the amendment within a maximum of 35 days from the date of receipt.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval for the research.

We are pleased to welcome researchers and R & D staff at our Research Ethics Service Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

17/NE/0352:	Please quote this number on all correspondence

Yours sincerely

Sarah Prothero

Sarah Prothero
REC Assistant

Email: nrescommittee.northeast-tyneandwearsouth@nhs.net

Copy to: *Professor Andrew MacLeod, Royal Holloway*

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Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

10 November 2017

Dr Freya Corfield
Doctorate in Clinical Psychology
Dept of Psychology
Royal Holloway
Egham TW20 0EX

Dear Dr Corfield

Study title:	**Validation of the IPAD version of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) against conventional paper BICAMS administration**
REC reference:	**17/NE/0352**
Protocol number:	**1**
IRAS project ID:	**233473**

The Proportionate Review Sub-Committee of the North East - Tyne & Wear South Research Ethics Committee reviewed the above application in correspondence.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact hra.studyregistration@nhs.net outlining the reasons for your request. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

On behalf of the Committee, the Sub-Committee gave a **Favourable** ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion").

Summary of discussion at the meeting

The Sub-Committee raised the following issues and you responded accordingly as follows.

Recruitment arrangements and access to health information, and fair participant selection

Further information was requested regarding the rationale for inclusion of participants in the study who have been "born and educated in England" and not any other English speaking country. A clear explanation was requested why only English speakers would be involved in the study.

You clarified that the rationale for only including participants who have been "born and educated in England" was to reduce the number of confounding variables in the study. The cognitive tests used in the current study were developed through assessment of a normative population with a similar educational and linguistic history, particularly the Test of Premorbid Functioning (TOPF). You added this reasoning to the protocol and information sheet and provided revised copies.

Informed consent process and the adequacy and completeness of participant information

The consent form should include the mandatory paragraph (as appropriate to this study) - 'I understand that relevant sections of my (medical records) and data collected during the study may be looked at by responsible individuals from the NHS Trust or from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records'.

You amended the consent form accordingly and provided a revised copy.

Favourable risk benefit ratio; anticipated benefit/risks for research participants (present and future)

The Committee also recommended that with regard to participants experiencing potential fatigue, it would be useful to consider if the testing time could be divided into two sessions (if the time for testing would allow for this).

You confirmed that participants would be offered the choice to divide the testing time into two sessions if they experience fatigue.

The Sub-Committee was satisfied with the responses given to the issues raised and also the revised documents.

In addition to the changes above, you noted the following clarifications/amendments in response to the issues raised by the HRA Assessor.

The participant information sheet was updated to include information regarding where patient identifiable data would be stored, the security arrangement in place for this, and how long this would be stored following completion of the study.

The consent form was revised to include a clause for allowing access to study/patient data for auditing/monitoring purposes.

The participant information sheet and consent form were updated with the IRAS ID.

You clarified that NHS indemnity had not been selected at A76-3 as data collection would be conducted at participants' homes not on NHS premises (although recruitment would be conducted at the NHS premises).

With regard to the loan of equipment to the site, you clarified that the academic supervisor Professor Dawn Langdon, would loan the IPAD to you as chief investigator for the period of data collection only. The IPAD would not be loaned to the site at any point.

With regard to security arrangements for transfer of patient identifiable data from the participating site to the sponsor, you clarified that data would be sent using your NHS.net to NHS.net account and that e-mails would be password protected.

With regard to anonymisation and a space for the patient's name on the Fatigue Severity Scale, you explained that this involved a pdf copy of a validated questionnaire hence no changes were made to the label and you confirmed that only the anonymised code would be used on the questionnaire.

Updated copies of the participant information sheet, consent form and protocol were provided accordingly.

The Sub-Committee noted the above.

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [Leaflet]	1	11 October 2017
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Indemnity]		01 August 2017
IRAS Application Form [IRAS_Form_24102017]		24 October 2017
Participant consent form [Consent Form]	2	03 November 2017
Participant information sheet (PIS) [Information Sheet]	2	03 November 2017
Research protocol or project proposal [Protocol]	2	03 November 2017
Summary CV for Chief Investigator (CI) [CV]	1	
Summary CV for supervisor (student research) [Langdon CV for IRAS]		
Summary, synopsis or diagram (flowchart) of protocol in non-technical language [Procedure Flowchart]	1	11 October 2017
Validated questionnaire [Fatigue Severity Scale]		
Validated questionnaire [Hospital Anxiety and Depression Scale]		

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

17/NE/0352 **Please quote this number on all correspondence**

Yours sincerely
pp

Mr Ian Campbell
Vice Chair

Email: nrescommittee.northeast-tyneandwearsouth@nhs.net

Enclosures: List of names and professions of members who took part in the review

'After ethical review – guidance for researchers' SL-AR2

Copy to: Ms Annette Lock – Research Dept, Royal Holloway University of London

Ms Elizabeth Clough – R&D Dept, Barts Health NHS Trust

North East - Tyne & Wear South Research Ethics Committee

Attendance at PRS Sub-Committee of the REC meeting on 3 November 2017 by correspondence

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr Ian Campbell (Vice Chair)	Pharmacy	Yes	
Mr David Hill	Retired Technical Director	Yes	
Miss Rachel Smith	Barrister	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Ms Gillian Mayer	REC Manager

A Research Ethics Committee established by the Health Research Authority

NHS
Health Research Authority

Dr Freya Corfield
Doctorate in Clinical Psychology, Department of Psychology
Royal Holloway
Egham
TW20 0EX

Email: hra.approval@nhs.net

10 November 2017

Dear Dr Corfield,

Letter of HRA Approval

Study title:	**Validation of the IPAD version of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) against conventional paper BICAMS administration**
IRAS project ID:	**233473**
Protocol number:	**1**
REC reference:	**17/NE/0352**
Sponsor	**Royal Holloway**

I am pleased to confirm that HRA Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *'After Ethical Review – guidance for sponsors and investigators'*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hso-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **233473**. Please quote this on all correspondence.

Yours sincerely

Rekha Keshvara
Senior Assessor

Email: hra.approval@nhs.net

Copy to: *Ms Annette Lock, Royal Holloway (Sponsor contact)*
Ms Elizabeth Clough, Barts Health NHS Trust (R&D contact)

[Removed from online version]

6.7. Research and Development Confirmation E-mail Correspondence

[Removed from online version]

6.8. Participant Information Sheet

Validation of the IPAD version of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)

Information Sheet

My name is Freya Corfield and I am a Trainee Clinical Psychologist studying at Royal Holloway, University of London. You have been invited to take part in a research study, which is being conducted as part of my Doctorate in Clinical Psychology. Before you decide to participate, I would like you to understand what the research will involve and why it is being conducted. Below you will be given some information about the research and then you will be able to decide if you would like to take part. Please read this information carefully. If you have any questions, then please contact me using the email address at the bottom of the page.

What is the purpose of this study?

This research aims to test the effectiveness of an IPAD-based battery of tests and short online directional reaction time (DRT) test as an assessment to measures cognition (i.e. thinking styles) in adults with Multiple Sclerosis (MS).

Who is eligible to take part?

You have been invited to take part because we would like to make sure that the IPAD and DRT assessment are good measures of cognition.

To take part in this study you will need to be

- aged 18-65;
- able to communicate fluently in English;
- born and educated in the UK
- able to give informed consent.

Unfortunately, if you have any other primary neurologic or psychiatric condition, including a history of a condition (e.g. head trauma) that may separately contribute to cognitive impairment or a primary neurodevelopmental disorders (e.g. autism spectrum disorder, fetal alcohol syndrome) and/or a sensorimotor impairment that would confound the testing media, then you will not be able to participate. Participants will need to be ‘born and educated in England’ to reduce the number of variables which may interfere with the interpretation of the results.

Do I have to take part?

No. It is your choice whether you participate or not and your participation is entirely voluntary. If you do decide to take part, then you are free to withdraw from the study at any time and you do not need to give a reason. If you decide that you want to withdraw then you can contact me with your name and I will delete your data. You will be able to withdraw up until the end of April 2018 when the data analysis for this study will be finalised.

What would taking part involve?

If you decide to take part, you will be asked to complete three brief questionnaires asking about your demographic details and levels of mood and fatigue. After this you will take part in six short tests which test your thinking styles by asking you to pronounce a list of words, sort pegs, decipher symptoms and remember information previously presented. Some tests will be timed and you will be informed if they are. It is estimated that the total time taken will be no longer than 90 minutes. At the end of the face-to-face assessment you will be provided with a token and a link for you to complete the online DRT in your own time. The DRT can be accessed via a browser on your smartphone, tablet or personal computer. The DRT takes less than 5 minutes to complete.

Are there any disadvantages or risks to taking part?

Although it is unlikely, it is possible that you may feel uncomfortable answering some of the questions you are asked or may find the questions distressing. If this is the case, the Patient Advice and Liaison Service at the Royal London Hospital – second floor central tower, near core lift 5 in the main building, is open 9:30am - 4:40pm Monday to Friday for independent advice. You are also free to not answer questions which you do not feel comfortable to. Your participation in this study will not affect your treatment as usual.

Are there any benefits to taking part and what will happen to the results?

It is hoped that this research will inform us about the how effective the test of cognition is in MS, since it is important to develop time and cost effective measures to administer in busy clinics. This research will contribute some understanding towards this. Unfortunately we are not able to give your individual scores, but you can request for a summary of the results when the research is completed. The results of the study will be written up as a doctoral thesis and submitted to an academic journal. The results may also be used in presentations about this work. The anonymised data will be entered into an international database for future meta-analysis. Importantly, all of the information you provide will remain anonymous.

Will my information remain confidential?

All of the information that you provide will remain anonymous. To keep your information confidential you will be assigned a unique identifying number. Individual responses will only be used by the researchers. The database will be stored on a password protected secure network folder on a Royal Holloway, University of London Computer accessed only by the Chief Investigator, Freya Corfield. Hard copies will be securely stored in locked filing cabinets in the Department of Clinical Psychology, Royal Holloway, University of London. The data will be stored up to 10 years for later analysis.

Who can I contact about the study?

If you have any questions about the study, please contact me using the following contact me using my e-mail address: freya.corfield.2015@live.rhul.ac.uk

If you have any concerns about how the study is being conducted, you can contact my supervisor using e-mail or telephone:

Prof. Dawn Langdon, d.langdon@rhul.ac.uk, 01784 443956

6.7. Consent Form

Validation of the IPAD version of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)

Consent Form

You have been invited to participate in a research study exploring the use of a test on an IPAD to assess thinking styles in Multiple Sclerosis (MS).

		Please initial
1.	I confirm that I have read the information sheet dated 4th January 2018 (version 3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw up until April 2018 without giving any reason, without my medical care or legal rights being affected.	☐
3.	I understand that relevant sections of my medical notes may be looked at by the Principal Investigator where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
4.	I understand that the information collected about me will be added to the research team's database to support research in the future	☐
5.	I understand that relevant sections of my medical records and data collected during the study may be looked at by responsible individuals from the NHS Trust or from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records	☐
5.	I allow access to study data for auditing and monitoring purposes	☐
6.	I agree to take part in the above study.	☐

Participant
Print Name: _____
Sign _____
Date _____
Person Taking Consent
Print Name: _____
Sign _____
Date _____

6.8. Fatigue Severity Scale (FSS)

[Removed from online version]

6.9. Hospital Anxiety and Depression Scale (HADS)

[Removed from online version]

6.10. Experience of BICAMS Survey

After completing the iPad BICAMS, please select which of the following best fits with your opinion

1. How easy did you find completing the test?

Not at all easy	Not easy	Neutral	Moderately easy	Very easy
☐	☐	☐	☐	☐

2. How enjoyable did you find completing the test?

Not at all enjoyable	Not enjoyable	Neutral	Moderately enjoyable	Very enjoyable
☐	☐	☐	☐	☐

After completing the paper and pencil BICAMS, please select which of the following best fits with your opinion

3. How easy did you find completing the test?

Not at all easy	Not easy	Neutral	Moderately easy	Very easy
☐	☐	☐	☐	☐

4. How enjoyable did you find completing the test?

Not at all enjoyable	Not enjoyable	Neutral	Moderately enjoyable	Very enjoyable
☐	☐	☐	☐	☐

5. After completing all of the tests, which type of BICAMS did you prefer to be tested by?

iPad	paper and pencil	No preference
☐	☐	☐

6. What was the reason for your choice?

7. Compared to the paper and pencil version, how would you feel about being tested using the i-pad BICAMS on a yearly basis in the future?

Very dissatisfied	Moderately dissatisfied	Slightly dissatisfied	Neutral	Slightly satisfied	Moderately satisfied	Very satisfied
☐	☐	☐	☐	☐	☐	☐

8. Any other feedback?

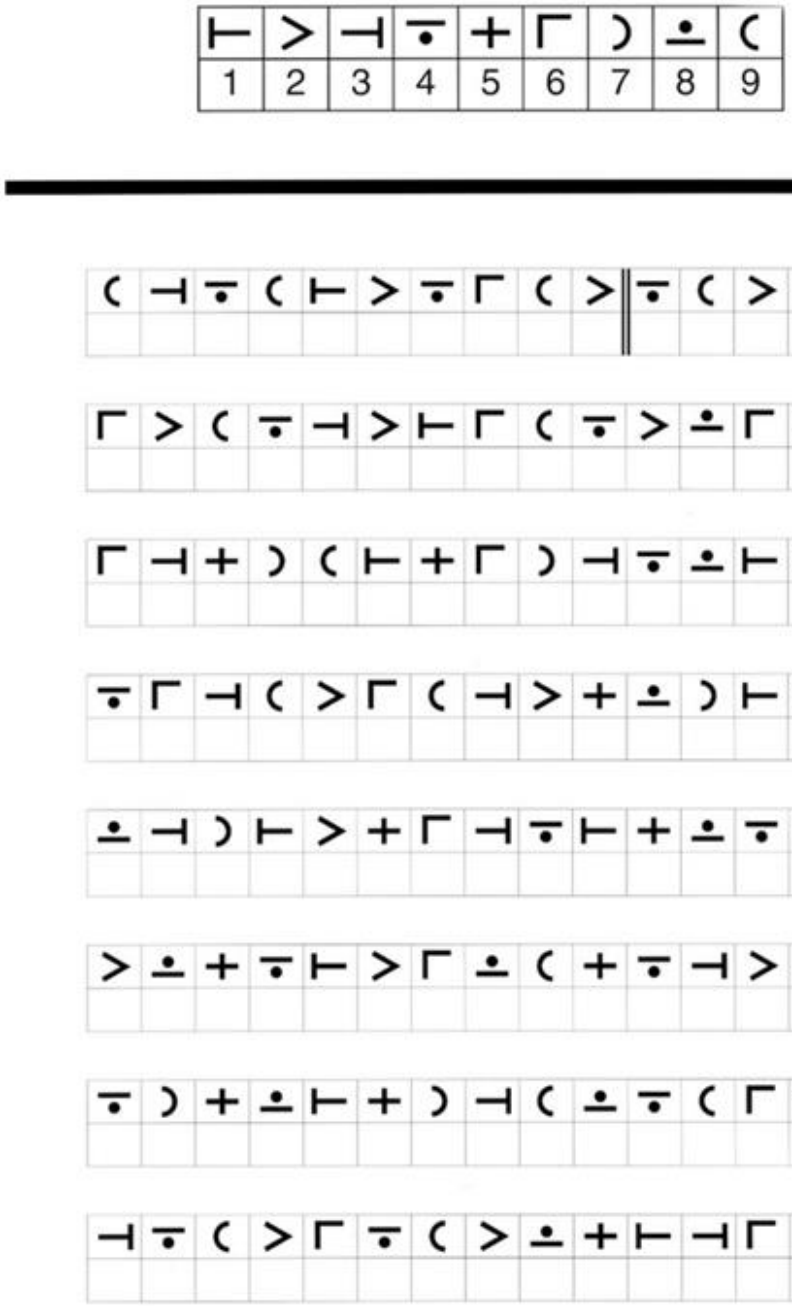
6.12. Nine Hole Peg Test (9HPT)

[Removed from online version]

6.13. Grooved Peg Test (GPT)

[Removed from online version]

6.14. BICAMS example Symbol Digit Modalities Test (SDMT)



Copied from Langdon et al., 2012, with permission from author

6.15. BICAMS example California Verbal Learning Trials II (CVLT-II)

Truck

Spinach

Giraffe

Bookcase

Onion

Motorcycle

Cabinet

Zebra

Coach

Lamp

Celery

Cow

Desk

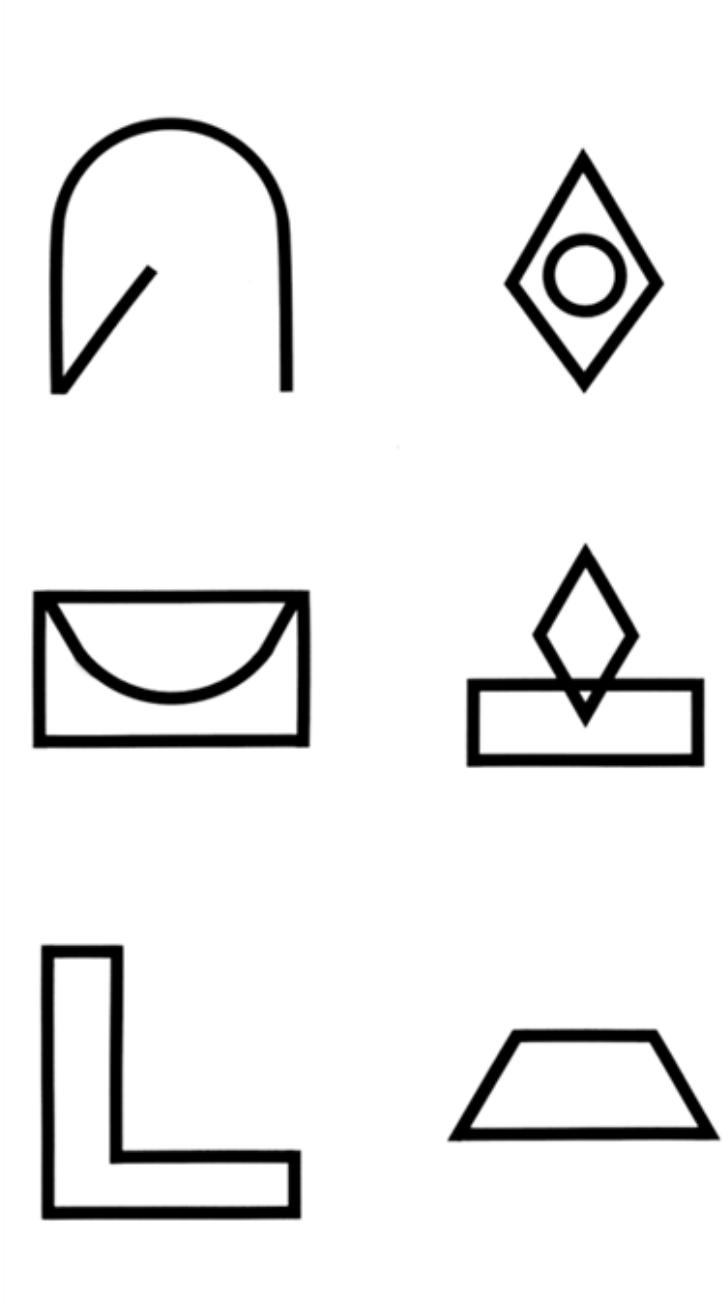
Boat

Squirrel

Cabbage

Copied from Langdon et al., 2012, with permission from author

6.16. BICAMS example Brief Visual Memory Test Revised learning trials (BVMT-R)



Copied from Langdon et al., 2012, with permission from author

6.17. BICAMS example of iPad screens

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